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(54) Title: NOVEL HUMAN KINASES AND POLYNUCLEOTIDES ENCODING THE SAME

(57) Abstract: Novel human polynucleotide and polypeptide sequences are disclosed that can be used in therapeutic, diagnostic, and pharmacogenomic applications.

NOVEL HUMAN KINASES AND POLYNUCLEOTIDES ENCODING THE SAME

The present application claims the benefit of U.S. Provisional Application Numbers 60/183,582 and 60/184,014 which were filed on February 18, 2000 and February 22, 2000, respectively, and are herein incorporated by reference in their entirety.

1. INTRODUCTION

The present invention relates to the discovery, identification, and characterization of novel human polynucleotides encoding proteins that share sequence similarity with mammalian transporter proteins. The invention encompasses the described polynucleotides, host cell expression systems, the encoded proteins, fusion proteins, polypeptides and peptides, antibodies to the encoded proteins and peptides, and genetically engineered animals that either lack or over express the disclosed sequences, antagonists and agonists of the proteins, and other compounds that modulate the expression or activity of the proteins encoded by the disclosed sequences that can be used for diagnosis, drug screening, clinical trial monitoring, and treatment of diseases and disorders.

2. BACKGROUND OF THE INVENTION

Kinases mediate phosphorylation of a wide variety of proteins and compounds in the cell. Along with phosphatases, kinases are involved in a range of regulatory pathways. Given the physiological importance of kinases, they have been subject to intense scrutiny and are proven drug targets.

3. SUMMARY OF THE INVENTION

The present invention relates to the discovery, identification, and characterization of nucleotides that encode novel human proteins and the corresponding amino acid sequences of

these proteins. The novel human proteins (NHPs) described for the first time herein share structural similarity with animal kinases, including, but not limited to cell division control protein kinases, serine/threonine protein kinases and membrane-associated guanylate kinases (MAGUKs). As such, the novel polynucleotides encode a novel kinase family having homologues and orthologs across a range of phyla and species.

The novel human polynucleotides described herein, encode open reading frames (ORFs) encoding proteins of 1,035, 1,214, 1,007, 296, 72, 318, 94, 108, 375, 137, 473, 249, 155, 184, 520, 296, 195, 224, 560, 336, 211, 240, 576, and 352 amino acids in length (see SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 and 48, respectively).

The invention also encompasses agonists and antagonists of the described NHPs, including small molecules, large molecules, mutant NHPs, or portions thereof, that compete with native NHP, peptides, and antibodies, as well as nucleotide sequences that can be used to inhibit the expression of the described NHPs (*e.g.*, antisense and ribozyme molecules, and gene or regulatory sequence replacement constructs) or to enhance the expression of the described NHP sequences (*e.g.*, expression constructs that place the described sequence under the control of a strong promoter system), and transgenic animals that express a NHP transgene, or "knock-outs" (which can be conditional) that do not express a functional NHP. Several knockout ES cell lines have been produced that contain gene trap mutations in murine homologs (or an ortholog of a human homolog) of the described sequences.

Further, the present invention also relates to processes for identifying compounds that modulate, *i.e.*, act as agonists or antagonists, of NHP expression and/or NHP activity that utilize purified preparations of the described NHPs and/or NHP product, or cells expressing the same. Such compounds can be used as

therapeutic agents for the treatment of any of a wide variety of symptoms associated with biological disorders or imbalances.

4. DESCRIPTION OF THE SEQUENCE LISTING AND FIGURES

The Sequence Listing provides the sequences of the described NHP ORFs that encode the described NHP amino acid sequences. Both SEQ ID NO:49 and SEQ ID NO:50 describe full length NHP ORFs as well as flanking 5' and 3' sequences.

5. DETAILED DESCRIPTION OF THE INVENTION

The NHP sequences described in SEQ ID NOS: 1-6 and SEQ ID NOS: 50, were compiled from gene trapped sequences in conjunction with sequences available in GENBANK. These NHPs, described for the first time herein, are novel proteins that are expressed *in, inter alia,* human cell lines, and human fetal brain, brain, pituitary, cerebellum, thymus, spleen, lymph node, bone marrow, trachea, kidney, liver, fetal liver, prostate, testis, thyroid, adrenal gland, pancreas, salivary gland, stomach, small intestine, colon, uterus, placenta, mammary gland, adipose, esophagus, bladder, cervix, rectum, pericardium, hypothalamus, ovary, fetal kidney, and fetal lung cells.

The NHP sequences described in SEQ ID NOS: 7-49 were compiled from gene trapped sequences in conjunction with sequences available in GENBANK, and cDNAs from lung and testis libraries (Edge Biosystems, Gaithersburg, MD). These NHPs, described for the first time herein, are novel proteins that are expressed *in, inter alia,* human cell lines, and human brain, pituitary, cerebellum, thymus, spleen, lymph node, bone marrow, trachea, kidney, liver, fetal liver, prostate, testis, adrenal gland, pancreas, salivary gland, stomach, small intestine, colon, skeletal muscle, uterus, placenta, mammary gland, adipose, skin, esophagus, bladder, rectum, thyroid, umbilical vein endothelial cells, and fetal lung cells.

The present invention encompasses the nucleotides presented in the Sequence Listing, host cells expressing such nucleotides, the expression products of such nucleotides, and: (a) nucleotides that encode mammalian homologs of the described sequences, including the specifically described NHPs, and the NHP products; (b) nucleotides that encode one or more portions of the NHPs that correspond to functional domains, and the polypeptide products specified by such nucleotide sequences, including but not limited to the novel regions of any active domain(s); (c) isolated nucleotides that encode mutant versions, engineered or naturally occurring, of the described NHPs in which all or a part of at least one domain is deleted or altered, and the polypeptide products specified by such nucleotide sequences, including but not limited to soluble proteins and peptides in which all or a portion of the signal sequence is deleted; (d) nucleotides that encode chimeric fusion proteins containing all or a portion of a coding region of an NHP, or one of its domains (*e.g.*, a receptor or ligand binding domain, accessory protein/self-association domain, etc.) fused to another peptide or polypeptide; or (e) therapeutic or diagnostic derivatives of the described polynucleotides such as oligonucleotides, antisense polynucleotides, ribozymes, dsRNA, or gene therapy constructs comprising a sequence first disclosed in the Sequence Listing.

As discussed above, the present invention includes: (a) the human DNA sequences presented in the Sequence Listing (and vectors comprising the same) and additionally contemplates any nucleotide sequence encoding a contiguous NHP open reading frame (ORF) that hybridizes to a complement of a DNA sequence presented in the Sequence Listing under highly stringent conditions, *e.g.*, hybridization to filter-bound DNA in 0.5 M $NaHPO_4$, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1xSSC/0.1% SDS at 68°C (Ausubel F.M. *et al.*, eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing

Associates, Inc., and John Wiley & sons, Inc., New York, at p. 2.10.3) and encodes a functionally equivalent gene product. Additionally contemplated are any nucleotide sequences that hybridize to the complement of a DNA sequence that encodes and expresses an amino acid sequence presented in the Sequence Listing under moderately stringent conditions, *e.g.*, washing in 0.2xSSC/0.1% SDS at 42°C (Ausubel et al., 1989, *supra*), yet still encodes a functionally equivalent NHP product. Functional equivalents of a NHP include naturally occurring NHPs present in other species and mutant NHPs whether naturally occurring or engineered (by site directed mutagenesis, gene shuffling, directed evolution as described in, for example, U.S. Patent No. 5,837,458). The invention also includes degenerate nucleic acid variants of the disclosed NHP polynucleotide sequences.

Additionally contemplated are polynucleotides encoding NHP ORFs, or their functional equivalents, encoded by polynucleotide sequences that are about 99, 95, 90, or about 85 percent similar or identical to corresponding regions of the nucleotide sequences of the Sequence Listing (as measured by BLAST sequence comparison analysis using, for example, the GCG sequence analysis package using standard default settings).

The invention also includes nucleic acid molecules, preferably DNA molecules, that hybridize to, and are therefore the complements of, the described NHP nucleotide sequences. Such hybridization conditions may be highly stringent or less highly stringent, as described above. In instances where the nucleic acid molecules are deoxyoligonucleotides ("DNA oligos"), such molecules are generally about 16 to about 100 bases long, or about 20 to about 80, or about 34 to about 45 bases long, or any variation or combination of sizes represented therein that incorporate a contiguous region of sequence first disclosed in the Sequence Listing. Such oligonucleotides can be used in conjunction with the polymerase chain reaction (PCR) to screen

libraries, isolate clones, and prepare cloning and sequencing templates, etc.

Alternatively, such NHP oligonucleotides can be used as hybridization probes for screening libraries, and assessing gene expression patterns (particularly using a micro array or high-throughput "chip" format). Additionally, a series of the described NHP oligonucleotide sequences, or the complements thereof, can be used to represent all or a portion of the described NHP sequences. An oligonucleotide or polynucleotide sequence first disclosed in at least a portion of one or more of the sequences of SEQ ID NOS: 1-50 can be used as a hybridization probe in conjunction with a solid support matrix/substrate (resins, beads, membranes, plastics, polymers, metal or metallized substrates, crystalline or polycrystalline substrates, etc.). Of particular note are spatially addressable arrays (*i.e.*, gene chips, microtiter plates, etc.) of oligonucleotides and polynucleotides, or corresponding oligopeptides and polypeptides, wherein at least one of the biopolymers present on the spatially addressable array comprises an oligonucleotide or polynucleotide sequence first disclosed in at least one of the sequences of SEQ ID NOS: 1-50, or an amino acid sequence encoded thereby. Methods for attaching biopolymers to, or synthesizing biopolymers on, solid support matrices, and conducting binding studies thereon are disclosed in, *inter alia*, U.S. Patent Nos. 5,700,637, 5,556,752, 5,744,305, 4,631,211, 5,445,934, 5,252,743, 4,713,326, 5,424,186, and 4,689,405 the disclosures of which are herein incorporated by reference in their entirety.

Addressable arrays comprising sequences first disclosed in SEQ ID NOS:1-50 can be used to identify and characterize the temporal and tissue specific expression of a gene. These addressable arrays incorporate oligonucleotide sequences of sufficient length to confer the required specificity, yet be within the limitations of the production technology. The length

of these probes is within a range of between about 8 to about 2000 nucleotides. Preferably the probes consist of 60 nucleotides and more preferably 25 nucleotides from the sequences first disclosed in SEQ ID NOS:1-50.

For example, a series of the described oligonucleotide sequences, or the complements thereof, can be used in chip format to represent all or a portion of the described sequences. The oligonucleotides, typically between about 16 to about 40 (or any whole number within the stated range) nucleotides in length can partially overlap each other and/or the sequence may be represented using oligonucleotides that do not overlap. Accordingly, the described polynucleotide sequences shall typically comprise at least about two or three distinct oligonucleotide sequences of at least about 8 nucleotides in length that are each first disclosed in the described Sequence Listing. Such oligonucleotide sequences can begin at any nucleotide present within a sequence in the Sequence Listing and proceed in either a sense (5'-to-3') orientation vis-a-vis the described sequence or in an antisense orientation.

Microarray-based analysis allows the discovery of broad patterns of genetic activity, providing new understanding of gene functions and generating novel and unexpected insight into transcriptional processes and biological mechanisms. The use of addressable arrays comprising sequences first disclosed in SEQ ID NOS:1-50 provides detailed information about transcriptional changes involved in a specific pathway, potentially leading to the identification of novel components or gene functions that manifest themselves as novel phenotypes.

Probes consisting of sequences first disclosed in SEQ ID NOS:1-50 can also be used in the identification, selection and validation of novel molecular targets for drug discovery. The use of these unique sequences permits the direct confirmation of drug targets and recognition of drug dependent changes in gene

expression that are modulated through pathways distinct from the drugs intended target. These unique sequences therefore also have utility in defining and monitoring both drug action and toxicity.

As an example of utility, the sequences first disclosed in SEQ ID NOS:1-50 can be utilized in microarrays or other assay formats, to screen collections of genetic material from patients who have a particular medical condition. These investigations can also be carried out using the sequences first disclosed in SEQ ID NOS:1-50 *in silico* and by comparing previously collected genetic databases and the disclosed sequences using computer software known to those in the art.

Thus the sequences first disclosed in SEQ ID NOS:1-50 can be used to identify mutations associated with a particular disease and also as a diagnostic or prognostic assay.

Although the presently described sequences have been specifically described using nucleotide sequence, it should be appreciated that each of the sequences can uniquely be described using any of a wide variety of additional structural attributes, or combinations thereof. For example, a given sequence can be described by the net composition of the nucleotides present within a given region of the sequence in conjunction with the presence of one or more specific oligonucleotide sequence(s) first disclosed in the SEQ ID NOS: 1-50. Alternatively, a restriction map specifying the relative positions of restriction endonuclease digestion sites, or various palindromic or other specific oligonucleotide sequences can be used to structurally describe a given sequence. Such restriction maps, which are typically generated by widely available computer programs (*e.g.*, the University of Wisconsin GCG sequence analysis package, SEQUENCHER 3.0, Gene Codes Corp., Ann Arbor, MI, etc.), can optionally be used in conjunction with one or more discrete nucleotide sequence(s) present in the sequence that can be described by the relative position of the sequence relatve to one or more

additional sequence(s) or one or more restriction sites present in the disclosed sequence.

For oligonucleotide probes, highly stringent conditions may refer, *e.g.*, to washing in 6xSSC/0.05% sodium pyrophosphate at 37°C (for 14-base oligos), 48°C (for 17-base oligos), 55°C (for 20-base oligos), and 60°C (for 23-base oligos). These nucleic acid molecules may encode or act as NHP gene antisense molecules, useful, for example, in NHP gene regulation (for and/or as antisense primers in amplification reactions of NHP gene nucleic acid sequences). With respect to NHP gene regulation, such techniques can be used to regulate biological functions. Further, such sequences may be used as part of ribozyme and/or triple helix sequences that are also useful for NHP gene regulation.

Inhibitory antisense or double stranded oligonucleotides can additionally comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide can also comprise at least one modified sugar moiety selected from the group including but not limited to arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide will comprise at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an α-anomeric oligonucleotide. An α-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other (Gautier *et al.*, 1987, Nucl. Acids Res. *15*:6625-6641). The oligonucleotide is a 2'-0-methylribonucleotide (Inoue *et al.*, 1987, Nucl. Acids Res. *15*:6131-6148), or a chimeric RNA-DNA analogue (Inoue *et al.*, 1987, FEBS Lett. *215*:327-330). Alternatively, double stranded RNA can be used to disrupt the expression and function of a targeted NHP.

Oligonucleotides of the invention can be synthesized by standard methods known in the art, *e.g.* by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides can be synthesized by the method of Stein *et al.* (1988, Nucl. Acids Res. *16*:3209), and methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin *et al.*, 1988, Proc. Natl. Acad. Sci. U.S.A. *85*:7448-7451), etc.

Low stringency conditions are well known to those of skill in the art, and will vary predictably depending on the specific organisms from which the library and the labeled sequences are derived. For guidance regarding such conditions see, for example,

Sambrook *et al.*, 1989, Molecular Cloning, A Laboratory Manual (and periodic updates thereof), Cold Springs Harbor Press, N.Y.; and Ausubel *et al.*, 1989, Current Protocols in Molecular Biology, Green Publishing Associates and Wiley Interscience, N.Y.

Alternatively, suitably labeled NHP nucleotide probes can be used to screen a human genomic library using appropriately stringent conditions or by PCR. The identification and characterization of human genomic clones is helpful for identifying polymorphisms (including, but not limited to, nucleotide repeats, microsatellite alleles, single nucleotide polymorphisms, or coding single nucleotide polymorphisms), determining the genomic structure of a given locus/allele, and designing diagnostic tests. For example, sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), etc., that can be used in diagnostics and pharmacogenomics.

Further, a NHP gene homolog can be isolated from nucleic acid from an organism of interest by performing PCR using two degenerate or "wobble" oligonucleotide primer pools designed on the basis of amino acid sequences within the NHP products disclosed herein. The template for the reaction may be total RNA, mRNA, and/or cDNA obtained by reverse transcription of mRNA prepared from human or non-human cell lines or tissue known or suspected to express an allele of a NHP gene.

The PCR product can be subcloned and sequenced to ensure that the amplified sequences represent the sequence of the desired NHP gene. The PCR fragment can then be used to isolate a full length cDNA clone by a variety of methods. For example, the amplified fragment can be labeled and used to screen a cDNA library, such as a bacteriophage cDNA library. Alternatively, the labeled fragment

can be used to isolate genomic clones via the screening of a genomic library.

PCR technology can also be used to isolate full length cDNA sequences. For example, RNA can be isolated, following standard procedures, from an appropriate cellular or tissue source (*i.e.*, one known, or suspected, to express a NHP gene). A reverse transcription (RT) reaction can be performed on the RNA using an oligonucleotide primer specific for the most 5' end of the amplified fragment for the priming of first strand synthesis. The resulting RNA/DNA hybrid may then be "tailed" using a standard terminal transferase reaction, the hybrid may be digested with RNase H, and second strand synthesis may then be primed with a complementary primer. Thus, cDNA sequences upstream of the amplified fragment can be isolated. For a review of cloning strategies that can be used, see *e.g.*, Sambrook *et al.*, 1989, *supra*.

A cDNA encoding a mutant NHP gene can be isolated, for example, by using PCR. In this case, the first cDNA strand may be synthesized by hybridizing an oligo-dT oligonucleotide to mRNA isolated from tissue known or suspected to be expressed in an individual putatively carrying a mutant NHP allele, and by extending the new strand with reverse transcriptase. The second strand of the cDNA is then synthesized using an oligonucleotide that hybridizes specifically to the 5' end of the normal gene. Using these two primers, the product is then amplified via PCR, optionally cloned into a suitable vector, and subjected to DNA sequence analysis through methods well known to those of skill in the art. By comparing the DNA sequence of the mutant NHP allele to that of a corresponding normal NHP allele, the mutation(s) responsible for the loss or alteration of function of the mutant NHP gene product can be ascertained.

Alternatively, a genomic library can be constructed using DNA obtained from an individual suspected of or known to carry a

mutant NHP allele (*e.g.*, a person manifesting a NHP-associated phenotype such as, for example, obesity, high blood pressure, connective tissue disorders, infertility, etc.), or a cDNA library can be constructed using RNA from a tissue known, or suspected, to express a mutant NHP allele. A normal NHP gene, or any suitable fragment thereof, can then be labeled and used as a probe to identify the corresponding mutant NHP allele in such libraries. Clones containing mutant NHP gene sequences can then be purified and subjected to sequence analysis according to methods well known to those skilled in the art.

Additionally, an expression library can be constructed utilizing cDNA synthesized from, for example, RNA isolated from a tissue known, or suspected, to express a mutant NHP allele in an individual suspected of or known to carry such a mutant allele. In this manner, gene products made by the putatively mutant tissue can be expressed and screened using standard antibody screening techniques in conjunction with antibodies raised against a normal NHP product, as described below. (For screening techniques, see, for example, Harlow, E. and Lane, eds., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Press, Cold Spring Harbor, NY).

Additionally, screening can be accomplished by screening with labeled NHP fusion proteins, such as, for example, alkaline phosphatase-NHP or NHP-alkaline phosphatase fusion proteins. In cases where a NHP mutation results in an expressed gene product with altered function (*e.g.*, as a result of a missense or a frameshift mutation), polyclonal antibodies to a NHP are likely to cross-react with a corresponding mutant NHP gene product. Library clones detected via their reaction with such labeled antibodies can be purified and subjected to sequence analysis according to methods well known in the art.

The invention also encompasses (a) DNA vectors that contain any of the foregoing NHP coding sequences and/or their complements

(*i.e.*, antisense); (b) DNA expression vectors that contain any of the foregoing NHP coding sequences operatively associated with a regulatory element that directs the expression of the coding sequences (for example, baculo virus as described in U.S. Patent No. 5,869,336 herein incorporated by reference); (c) genetically engineered host cells that contain any of the foregoing NHP coding sequences operatively associated with a regulatory element that directs the expression of the coding sequences in the host cell; and (d) genetically engineered host cells that express an endogenous NHP gene under the control of an exogenously introduced regulatory element (*i.e.*, gene activation). As used herein, regulatory elements include, but are not limited to, inducible and non-inducible promoters, enhancers, operators and other elements known to those skilled in the art that drive and regulate expression. Such regulatory elements include but are not limited to the cytomegalovirus (hCMV) immediate early gene, regulatable, viral elements (particularly retroviral LTR promoters), the early or late promoters of SV40 adenovirus, the *lac* system, the *trp* system, the *TAC* system, the *TRC* system, the major operator and promoter regions of phage lambda, the control regions of fd coat protein, the promoter for 3-phosphoglycerate kinase (PGK), the promoters of acid phosphatase, and the promoters of the yeast α-mating factors.

The present invention also encompasses antibodies and anti-idiotypic antibodies (including Fab fragments), antagonists and agonists of the NHP, as well as compounds or nucleotide constructs that inhibit expression of a NHP gene (transcription factor inhibitors, antisense and ribozyme molecules, or gene or regulatory sequence replacement constructs), or promote the expression of a NHP (*e.g.*, expression constructs in which NHP coding sequences are operatively associated with expression control elements such as promoters, promoter/enhancers, etc.).

The NHPs or NHP peptides, NHP fusion proteins, NHP nucleotide sequences, antibodies, antagonists and agonists can be useful for the detection of mutant NHPs or inappropriately expressed NHPs for the diagnosis of disease. The NHP proteins or peptides, NHP fusion proteins, NHP nucleotide sequences, host cell expression systems, antibodies, antagonists, agonists and genetically engineered cells and animals can be used for screening for drugs (or high throughput screening of combinatorial libraries) effective in the treatment of the symptomatic or phenotypic manifestations of perturbing the normal function of NHP in the body. The use of engineered host cells and/or animals may offer an advantage in that such systems allow not only for the identification of compounds that bind to the endogenous receptor for an NHP, but can also identify compounds that trigger NHP-mediated activities or pathways.

Finally, the NHP products can be used as therapeutics. For example, soluble derivatives such as NHP peptides/domains corresponding to NHPs, NHP fusion protein products (especially NHP-Ig fusion proteins, *i.e.*, fusions of a NHP, or a domain of a NHP, to an IgFc), NHP antibodies and anti-idiotypic antibodies (including Fab fragments), antagonists or agonists (including compounds that modulate or act on downstream targets in a NHP-mediated pathway) can be used to directly treat diseases or disorders. For instance, the administration of an effective amount of soluble NHP, or a NHP-IgFc fusion protein or an anti-idiotypic antibody (or its Fab) that mimics the NHP could activate or effectively antagonize the endogenous NHP receptor. Nucleotide constructs encoding such NHP products can be used to genetically engineer host cells to express such products *in vivo;* these genetically engineered cells function as "bioreactors" in the body delivering a continuous supply of a NHP, a NHP peptide, or a NHP fusion protein to the body. Nucleotide constructs encoding functional NHPs, mutant NHPs, as well as antisense and ribozyme

molecules can also be used in "gene therapy" approaches for the modulation of NHP expression. Thus, the invention also encompasses pharmaceutical formulations and methods for treating biological disorders.

Various aspects of the invention are described in greater detail in the subsections below.

5.1 THE NHP SEQUENCES

The cDNA sequences and corresponding deduced amino acid sequences of the described NHPs are presented in the Sequence Listing. The NHP nucleotide sequences SEQ ID NOS:1-6 were obtained using the sequence information present in human gene trapped sequence tags.

Expression analysis has provided evidence that the described NHPs can be expressed in human tissues as well as gene trapped human cells. In addition to serine/threonine kinases, the NHPs described in SEQ ID NOS: 1-6 also share significant similarity to a range of additional kinase families such as NEK2 and NY-REN-55 as well as protein kinases from a range of phyla and species.

Likewise, the NHPs described in SEQ ID NOS: 7-49 share significant similarity to a range of additional kinase families from a variety of phyla and species, in addition to aforementioned MAGUKs. Two polymorphisms were identified during the sequencing project. The first identified a possible A-G transition at the sequence position corresponding to, for example, nucleotide 739 of SED ID NO: 7 (resulting in a ile-val change at corresponding amino acid position number 247 of, for example, SEQ ID NO:8). Another A-G transition was identified at the sequence position corresponding to, for example, nucleotide 67 of SED ID NO:9 (resulting in a ile-val change at corresponding amino acid position number 23 of, for example, SEQ ID NO: 10).

Given the physiological importance of protein kinases, they have been subject to intense scrutiny as exemplified and discussed

in U.S. Patent Nos. 5,817,479 and 5,817,479 which describe a variety of uses and applications that can be applied to the described NHP sequences and which are herein incorporated by reference in their entirety.

5.2 NHPS AND NHP POLYPEPTIDES

NHPs, polypeptides, peptide fragments, mutated, truncated, or deleted forms of the NHPs, and/or NHP fusion proteins can be prepared for a variety of uses. These uses include but are not limited to the generation of antibodies, as reagents in diagnostic assays, the identification of other cellular gene products related to a NHP, as reagents in assays for screening for compounds that can be used as pharmaceutical reagents useful in the therapeutic treatment of mental, biological, or medical disorders and diseases. Given the similarity information and expression data, the described NHPs can be targeted (by drugs, oligos, antibodies, etc,) in order to treat disease, or to therapeutically augment the efficacy of, for example, chemotherapeutic agents used in the treatment of breast or prostate cancer.

The Sequence Listing discloses the amino acid sequences encoded by the described NHP sequences. The NHPs typically display have initiator methionines in DNA sequence contexts consistent with a translation initiation site.

The NHP amino acid sequences of the invention include the amino acid sequence presented in the Sequence Listing as well as analogues and derivatives thereof. Further, corresponding NHP homologues from other species are encompassed by the invention. In fact, any NHP protein encoded by the NHP nucleotide sequences described above are within the scope of the invention, as are any novel polynucleotide sequences encoding all or any novel portion of an amino acid sequence presented in the Sequence Listing. The degenerate nature of the genetic code is well known, and, accordingly, each amino acid presented in the Sequence Listing, is

generically representative of the well known nucleic acid "triplet" codon, or in many cases codons, that can encode the amino acid. As such, as contemplated herein, the amino acid sequences presented in the Sequence Listing, when taken together with the genetic code (see, for example, Table 4-1 at page 109 of "Molecular Cell Biology", 1986, J. Darnell *et al.* eds., Scientific American Books, New York, NY, herein incorporated by reference) are generically representative of all the various permutations and combinations of nucleic acid sequences that can encode such amino acid sequences.

The invention also encompasses proteins that are functionally equivalent to the NHPs encoded by the presently described nucleotide sequences as judged by any of a number of criteria, including, but not limited to, the ability to bind and cleave a substrate of a NHP, or the ability to effect an identical or complementary downstream pathway, or a change in cellular metabolism (*e.g.*, proteolytic activity, ion flux, tyrosine phosphorylation, etc.). Such functionally equivalent NHP proteins include, but are not limited to, additions or substitutions of amino acid residues within the amino acid sequence encoded by the NHP nucleotide sequences described above, but which result in a silent change, thus producing a functionally equivalent gene product. Amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues involved. For example, nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine; positively charged (basic) amino acids include arginine, lysine, and histidine; and negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

A variety of host-expression vector systems can be used to express the NHP nucleotide sequences of the invention. Where, as in the present instance, the NHP peptide or polypeptide is thought to be membrane protein, the hydrophobic regions of the protein can be excised and the resulting soluble peptide or polypeptide can be recovered from the culture media. Such expression systems also encompass engineered host cells that express a NHP, or functional equivalent, *in situ*. Purification or enrichment of a NHP from such expression systems can be accomplished using appropriate detergents and lipid micelles and methods well known to those skilled in the art. However, such engineered host cells themselves may be used in situations where it is important not only to retain the structural and functional characteristics of the NHP, but to assess biological activity, *e.g.*, in drug screening assays.

The expression systems that may be used for purposes of the invention include but are not limited to microorganisms such as bacteria (*e.g.*, *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing NHP nucleotide sequences; yeast (*e.g.*, *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing NHP nucleotide sequences; insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing NHP sequences; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing NHP nucleotide sequences; or mammalian cell systems (*e.g.*, COS, CHO, BHK, 293, 3T3) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian

viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the NHP product being expressed. For example, when a large quantity of such a protein is to be produced for the generation of pharmaceutical compositions of or containing NHP, or for raising antibodies to a NHP, vectors that direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther *et al.*, 1983, EMBO J. *2*:1791), in which a NHP coding sequence may be ligated individually into the vector in frame with the *lacZ* coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, 1985, Nucleic Acids Res. *13*:3101-3109; Van Heeke & Schuster, 1989, J. Biol. Chem. *264*:5503-5509); and the like. pGEX vectors (Pharmacia or American Type Culture Collection) can also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. The PGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, *Autographa californica* nuclear polyhidrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. A NHP coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter). Successful insertion of NHP coding sequence will result in inactivation of the polyhedrin gene and production of

non-occluded recombinant virus (*i.e.*, virus lacking the proteinaceous coat coded for by the polyhedrin gene). These recombinant viruses are then used to infect Spodoptera frugiperda cells in which the inserted gene is expressed (*e.g.*, see Smith *et al.*, 1983, J. Virol. *46*:584; Smith, U.S. Patent No. 4,215,051).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the NHP nucleotide sequence of interest may be ligated to an adenovirus transcription/translation control complex, *e.g.*, the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (*e.g.*, region E1 or E3) will result in a recombinant virus that is viable and capable of expressing a NHP product in infected hosts (*e.g.*, See Logan & Shenk, 1984, Proc. Natl. Acad. Sci. USA *81*:3655-3659). Specific initiation signals may also be required for efficient translation of inserted NHP nucleotide sequences. These signals include the ATG initiation codon and adjacent sequences. In cases where an entire NHP gene or cDNA, including its own initiation codon and adjacent sequences, is inserted into the appropriate expression vector, no additional translational control signals may be needed. However, in cases where only a portion of a NHP coding sequence is inserted, exogenous translational control signals, including, perhaps, the ATG initiation codon, must be provided. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements,

transcription terminators, etc. (See Bitter *et al.*, 1987, Methods in Enzymol. *153*:516-544).

In addition, a host cell strain may be chosen that modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include, but are not limited to, CHO, VERO, BHK, HeLa, COS, MDCK, 293, 3T3, WI38, and in particular, human cell lines.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the NHP sequences described above can be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (*e.g.*, promoter, enhancer sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer

cell lines which express the NHP product. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that affect the endogenous activity of the NHP product.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler, *et al.*, 1977, Cell *11*:223), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, 1962, Proc. Natl. Acad. Sci. USA *48*:2026), and adenine phosphoribosyltransferase (Lowy, *et al.*, 1980, Cell *22*:817) genes can be employed in tk^-, $hgprt^-$ or $aprt^-$ cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler, *et al.*, 1980, Natl. Acad. Sci. USA 77:3567; O'Hare, *et al.*, 1981, Proc. Natl. Acad. Sci. USA *78*:1527); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, Proc. Natl. Acad. Sci. USA *78*:2072); neo, which confers resistance to the aminoglycoside G-418 (Colberre-Garapin, *et al.*, 1981, J. Mol. Biol. *150*:1); and hygro, which confers resistance to hygromycin (Santerre, *et al.*, 1984, Gene *30*:147).

Alternatively, any fusion protein can be readily purified by utilizing an antibody specific for the fusion protein being expressed. For example, a system described by Janknecht *et al.* allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht, *et al.*, 1991, Proc. Natl. Acad. Sci. USA *88*:8972-8976). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the gene's open reading frame is translationally fused to an amino-terminal tag consisting of six histidine residues. Extracts from cells infected with recombinant vaccinia virus are loaded onto Ni^{2+} nitriloacetic acid-agarose columns and histidine-tagged proteins are selectively eluted with imidazole-containing buffers.

Also encompassed by the present invention are fusion proteins that direct the NHP to a target organ and/or facilitate transport across the membrane into the cytosol. Conjugation of NHPs to antibody molecules or their Fab fragments could be used to target cells bearing a particular epitope. Attaching the appropriate signal sequence to the NHP would also transport the NHP to the desired location within the cell. Alternatively targeting of NHP or its nucleic acid sequence might be achieved using liposome or lipid complex based delivery systems. Such technologies are described in Liposomes:A Practical Approach, New, RRC ed., Oxford University Press, New York and in U.S. Patents Nos. 4,594,595, 5,459,127, 5,948,767 and 6,110,490 and their respective disclosures which are herein incorporated by reference in their entirety. Additionally embodied are novel protein constructs engineered in such a way that they facilitate transport of the NHP to the target site or desired organ, where they cross the cell membrane and/or the nucleus where the NHP can exert its functional activity. This goal may be achieved by coupling of the NHP to a cytokine or other ligand that provides targeting specificity, and/or to a protein transducing domain (see generally U.S. applications Ser. No. 60/111,701 and 60/056,713, both of which are herein incorporated by reference, for examples of such transducing sequences) to facilitate passage across cellular membranes and can optionally be engineered to include nuclear localization sequences.

5.3 ANTIBODIES TO NHP PRODUCTS

Antibodies that specifically recognize one or more epitopes of a NHP, or epitopes of conserved variants of a NHP, or peptide fragments of a NHP are also encompassed by the invention. Such antibodies include but are not limited to polyclonal antibodies, monoclonal antibodies (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, $F(ab')_2$ fragments,

fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above.

The antibodies of the invention may be used, for example, in the detection of NHP in a biological sample and may, therefore, be utilized as part of a diagnostic or prognostic technique whereby patients may be tested for abnormal amounts of NHP. Such antibodies may also be utilized in conjunction with, for example, compound screening schemes for the evaluation of the effect of test compounds on expression and/or activity of a NHP gene product. Additionally, such antibodies can be used in conjunction gene therapy to, for example, evaluate the normal and/or engineered NHP-expressing cells prior to their introduction into the patient. Such antibodies may additionally be used as a method for the inhibition of abnormal NHP activity. Thus, such antibodies may, therefore, be utilized as part of treatment methods.

For the production of antibodies, various host animals may be immunized by injection with a NHP, an NHP peptide (*e.g.*, one corresponding to a functional domain of an NHP), truncated NHP polypeptides (NHP in which one or more domains have been deleted), functional equivalents of the NHP or mutated variant of the NHP. Such host animals may include but are not limited to pigs, rabbits, mice, goats, and rats, to name but a few. Various adjuvants may be used to increase the immunological response, depending on the host species, including but not limited to Freund's adjuvant (complete and incomplete), mineral salts such as aluminum hydroxide or aluminum phosphate, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and *Corynebacterium parvum*. Alternatively, the immune response could be enhanced by combination and or coupling with molecules such as keyhole limpet

hemocyanin, tetanus toxoid, diptheria toxoid, ovalbumin, cholera toxin or fragments thereof. Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of the immunized animals.

Monoclonal antibodies, which are homogeneous populations of antibodies to a particular antigen, can be obtained by any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique of Kohler and Milstein, (1975, Nature *256*:495-497; and U.S. Patent No. 4,376,110), the human B-cell hybridoma technique (Kosbor *et al.*, 1983, Immunology Today *4*:72; Cole *et al.*, 1983, Proc. Natl. Acad. Sci. USA *80*:2026-2030), and the EBV-hybridoma technique (Cole *et al.*, 1985, Monoclonal Antibodies And Cancer Therapy, Alan R. Liss, Inc., pp. 77-96). Such antibodies may be of any immunoglobulin class including IgG, IgM, IgE, IgA, IgD and any subclass thereof. The hybridoma producing the mAb of this invention may be cultivated *in vitro* or *in vivo*. Production of high titers of mAbs in vivo makes this the presently preferred method of production.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison *et al.*, 1984, Proc. Natl. Acad. Sci., *81*:6851-6855; Neuberger *et al.*, 1984, Nature, *312*:604-608; Takeda *et al.*, 1985, Nature, *314*:452-454) by splicing the genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. Such technologies are described in U.S. Patents Nos. 6,075,181 and 5,877,397 and their respective disclosures which are herein incorporated by reference in their entirety. Also encompassed by

the present invention is the use of fully humanized monoclonal antibodies as described in US Patent No. 6,150,584 and respective disclosures which are herein incorporated by reference in their entirety.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent 4,946,778; Bird, 1988, Science *242*:423-426; Huston *et al.*, 1988, Proc. Natl. Acad. Sci. USA *85*:5879-5883; and Ward *et al.*, 1989, Nature *341*:544-546) can be adapted to produce single chain antibodies against NHP gene products. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, such fragments include, but are not limited to: the $F(ab')_2$ fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the $F(ab')_2$ fragments. Alternatively, Fab expression libraries may be constructed (Huse *et al.*, 1989, Science, *246*:1275-1281) to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity.

Antibodies to a NHP can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" a given NHP, using techniques well known to those skilled in the art. (See, *e.g.*, Greenspan & Bona, 1993, FASEB J *7(5)*:437-444; and Nissinoff, 1991, J. Immunol. *147(8)*:2429-2438). For example antibodies which bind to a NHP domain and competitively inhibit the binding of NHP to its cognate receptor can be used to generate anti-idiotypes that "mimic" the NHP and, therefore, bind and activate or neutralize a receptor. Such anti-idiotypic antibodies or Fab fragments of such anti-idiotypes can be used in therapeutic regimens involving a NHP mediated pathway.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims. All cited publications, patents, and patent applications are herein incorporated by reference in their entirety.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule comprising at least 24 contiguous bases of nucleotide sequence first disclosed in SEQ ID NO: 1.

2. An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO: 2; and

(b) hybridizes under stringent conditions to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof.

3. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:2.

4. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:4.

5. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:6.

6. An isolated nucleic acid molecule comprising at least 24 contiguous bases of nucleotide sequence first disclosed in SEQ ID NO: 45.

7. An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO: 46; and

(b) hybridizes under stringent conditions to the nucleotide sequence of SEQ ID NO: 45 or the complement thereof.

8. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:46.

9. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:38.

10. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:30

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Ala Ser Pro Gln Met Ser Leu Lys Leu Glu Gly Asn Leu Glu Glu Pro
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Asp Asp Leu Glu Thr Glu Ile Leu Gln Glu Pro Ser Gly Thr Asn Lys
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Asp Glu Ser Leu Pro Cys Thr Ile Thr Asp Val Trp Ile Ser Glu Glu
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Lys Glu Thr Lys Glu Thr Gln Ser Ala Asp Arg Ile Thr Ile Gln Glu
705                 710                 715                 720
Asn Glu Val Ser Glu Asp Gly Val Ser Ser Thr Val Asp Gln Leu Ser
                725                 730                 735
Asp Ile His Ile Glu Pro Gly Thr Asn Asp Ser Gln His Ser Lys Cys
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Asp Val Asp Lys Ser Val Gln Pro Glu Pro Phe Phe His Lys Val Val
        755                 760                 765
His Ser Glu His Leu Asn Leu Val Pro Gln Val Gln Ser Val Gln Cys
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Ser Pro Glu Glu Ser Phe Ala Phe Arg Ser His Ser His Leu Pro Pro
785                 790                 795                 800
Lys Asn Lys Asn Lys Asn Ser Leu Leu Ile Gly Leu Ser Thr Gly Leu
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Phe Asp Ala Asn Asn Pro Lys Met Leu Arg Thr Cys Ser Leu Pro Asp
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Leu Ser Lys Leu Phe Arg Thr Leu Met Asp Val Pro Thr Val Gly Asp
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Val Arg Gln Asp Asn Leu Glu Ile Asp Glu Ile Lys Asp Glu Asn Ile
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Lys Glu Gly Pro Ser Asp Ser Glu Asp Ile Val Phe Glu Glu Thr Asp
865                 870                 875                 880
Thr Asp Leu Gln Glu Leu Gln Ala Ser Met Glu Gln Leu Leu Arg Glu
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Gln Pro Gly Glu Glu Tyr Ser Glu Glu Glu Glu Ser Val Leu Lys Asn
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Ser Asp Val Glu Pro Thr Ala Asn Gly Thr Asp Val Ala Asp Glu Asp
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Asp Asn Pro Ser Ser Glu Ser Ala Leu Asn Glu Glu Trp His Ser Asp
    930                 935                 940
Asn Ser Asp Gly Glu Ile Ala Ser Glu Cys Glu Cys Asp Ser Val Phe
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Asn His Leu Glu Glu Leu Arg Leu His Leu Glu Gln Glu Met Gly Phe
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Glu Lys Phe Phe Glu Val Tyr Glu Lys Ile Lys Ala Ile His Glu Asp
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Glu Asp Glu Asn Ile Glu Ile Cys Ser Lys Ile Val Gln Asn Ile Leu
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Gly Asn Glu His Gln His Leu Tyr Ala Lys Ile Leu His Leu Val Met
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<213> homo sapiens

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35 40 45
Arg Arg Glu Val Ala Val Leu Ala Asn Met Lys His Pro Asn Ile Val
50 55 60
Gln Tyr Arg Glu Ser Phe Glu Glu Asn Gly Ser Leu Tyr Ile Val Met
65 70 75 80
Asp Tyr Cys Glu Gly Gly Asp Leu Phe Lys Arg Ile Asn Ala Gln Lys
85 90 95
Gly Val Leu Phe Gln Glu Asp Gln Ile Leu Asp Trp Phe Val Gln Ile
100 105 110
Cys Leu Ala Leu Lys His Val His Asp Arg Lys Ile Leu His Arg Asp
115 120 125
Ile Lys Ser Gln Asn Ile Phe Leu Thr Lys Asp Gly Thr Val Gln Leu
130 135 140
Gly Asp Phe Gly Ile Ala Arg Val Leu Asn Ser Thr Val Glu Leu Ala
145 150 155 160
Arg Thr Cys Ile Gly Thr Pro Tyr Tyr Leu Ser Pro Glu Ile Cys Glu
165 170 175
Asn Lys Pro Tyr Asn Asn Lys Ser Asp Ile Trp Ala Leu Gly Cys Val
180 185 190
Leu Tyr Glu Leu Cys Thr Leu Lys His Ala Phe Glu Ala Gly Ser Met
195 200 205
Lys Asn Leu Val Leu Lys Ile Ile Ser Gly Ser Phe Pro Pro Val Ser
210 215 220
Leu His Tyr Ser Tyr Asp Leu Arg Ser Leu Val Ser Gln Leu Phe Lys
225 230 235 240
Arg Asn Pro Arg Asp Arg Pro Ser Val Asn Ser Ile Leu Glu Lys Gly
245 250 255
Phe Ile Ala Lys Arg Ile Glu Lys Phe Leu Ser Pro Gln Leu Ile Ala
260 265 270
Glu Glu Phe Cys Leu Lys Thr Phe Ser Lys Phe Gly Ser Gln Pro Ile
275 280 285
Pro Ala Lys Arg Pro Ala Ser Gly Gln Asn Ser Ile Ser Val Met Pro
290 295 300
Ala Gln Lys Ile Thr Lys Pro Ala Ala Lys Tyr Gly Ile Pro Leu Ala
305 310 315 320
Tyr Lys Lys Tyr Gly Asp Lys Lys Leu His Glu Lys Lys Pro Leu Gln
325 330 335
Lys His Lys Gln Ala His Gln Thr Pro Glu Lys Arg Val Asn Thr Gly
340 345 350
Glu Glu Arg Arg Lys Ile Ser Glu Glu Ala Ala Arg Lys Arg Arg Leu
355 360 365
Glu Phe Ile Glu Lys Glu Lys Lys Gln Lys Asp Gln Ile Ile Ser Leu

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Gly Ser Gly Glu Val Lys Ala Pro Phe Leu Gly Ser Gly Gly Thr Ile
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Ala Pro Ser Ser Phe Ser Ser Arg Gly Gln Tyr Glu His Tyr His Ala
        435                 440                 445
Ile Phe Asp Gln Met Gln Gln Gln Arg Ala Glu Asp Asn Glu Ala Lys
    450                 455                 460
Trp Lys Arg Glu Ile Tyr Gly Arg Gly Leu Pro Glu Arg Gln Lys Gly
465                 470                 475                 480
Gln Leu Ala Val Glu Arg Ala Lys Gln Val Glu Glu Phe Leu Gln Arg
                485                 490                 495
Lys Arg Glu Ala Met Gln Asn Lys Ala Arg Ala Glu Gly His Met Val
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Tyr Leu Ala Arg Leu Arg Gln Ile Arg Leu Gln Asn Phe Asn Glu Arg
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Gln Gln Ile Lys Ala Lys Leu Arg Gly Glu Lys Lys Glu Ala Asn His
    530                 535                 540
Ser Glu Gly Gln Glu Gly Ser Glu Glu Ala Asp Met Arg Arg Lys Lys
545                 550                 555                 560
Ile Glu Ser Leu Lys Ala His Ala Asn Ala Arg Ala Ala Val Leu Lys
                565                 570                 575
Glu Gln Leu Glu Arg Lys Arg Lys Glu Ala Tyr Glu Arg Glu Lys Lys
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Val Trp Glu Glu His Leu Val Ala Lys Gly Val Lys Ser Ser Asp Val
        595                 600                 605
Ser Pro Pro Leu Gly Gln His Glu Thr Gly Gly Ser Pro Ser Lys Gln
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Gln Met Arg Ser Val Ile Ser Val Thr Ser Ala Leu Lys Glu Val Gly
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Val Asp Ser Ser Leu Thr Asp Thr Arg Glu Thr Ser Glu Glu Met Gln
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Lys Thr Asn Asn Ala Ile Ser Ser Lys Arg Glu Ile Leu Arg Arg Leu
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Asn Glu Asn Leu Lys Ala Gln Glu Asp Glu Lys Gly Met Gln Asn Leu
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Ser Asp Thr Phe Glu Ile Asn Val His Glu Asp Ala Lys Glu His Glu
    690                 695                 700
Lys Glu Lys Ser Val Ser Ser Asp Arg Lys Lys Trp Glu Ala Gly Gly
705                 710                 715                 720
Gln Leu Val Ile Pro Leu Asp Glu Leu Thr Leu Asp Thr Ser Phe Ser
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Thr Thr Glu Arg His Thr Val Gly Glu Val Ile Lys Leu Gly Pro Asn
            740                 745                 750
Gly Ser Pro Arg Arg Ala Trp Gly Lys Ser Pro Thr Asp Ser Val Leu
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Lys Ile Leu Gly Glu Ala Glu Leu Gln Leu Gln Thr Glu Leu Leu Glu
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Asn Thr Thr Ile Arg Ser Glu Ile Ser Pro Glu Gly Glu Lys Tyr Lys
785                 790                 795                 800
Pro Leu Ile Thr Gly Glu Lys Lys Val Gln Cys Ile Ser His Glu Ile
                805                 810                 815
Asn Pro Ser Ala Ile Val Asp Ser Pro Val Glu Thr Lys Ser Pro Glu
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Thr Asn Lys Asp Glu Ser Leu Pro Cys Thr Ile Thr Asp Val Trp Ile
865                 870                 875                 880
Ser Glu Glu Lys Glu Thr Lys Glu Thr Gln Ser Ala Asp Arg Ile Thr
                885                 890                 895
Ile Gln Glu Asn Glu Val Ser Glu Asp Gly Val Ser Ser Thr Val Asp
            900                 905                 910
Gln Leu Ser Asp Ile His Ile Glu Pro Gly Thr Asn Asp Ser Gln His
        915                 920                 925
Ser Lys Cys Asp Val Asp Lys Ser Val Gln Pro Glu Pro Phe Phe His
    930                 935                 940
Lys Val Val His Ser Glu His Leu Asn Leu Val Pro Gln Val Gln Ser
945                 950                 955                 960
Val Gln Cys Ser Pro Glu Glu Ser Phe Ala Phe Arg Ser His Ser His
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Leu Pro Pro Lys Asn Lys Asn Lys Asn Ser Leu Leu Ile Gly Leu Ser
            980                 985                 990
Thr Gly Leu Phe Asp Ala Asn Asn Pro Lys Met Leu Arg Thr Cys Ser
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Leu Pro Asp Leu Ser Lys Leu Phe Arg Thr Leu Met Asp Val Pro Thr
    1010                1015                1020
Val Gly Asp Val Arg Gln Asp Asn Leu Glu Ile Asp Glu Ile Lys Asp
1025                1030                1035                1040
Glu Asn Ile Lys Glu Gly Pro Ser Asp Ser Glu Asp Ile Val Phe Glu
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Glu Thr Asp Thr Asp Leu Gln Glu Leu Gln Ala Ser Met Glu Gln Leu
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Leu Arg Glu Gln Pro Gly Glu Glu Tyr Ser Glu Glu Glu Glu Ser Val
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Leu Lys Asn Ser Asp Val Glu Pro Thr Ala Asn Gly Thr Asp Val Ala
    1090                1095                1100
Asp Glu Asp Asp Asn Pro Ser Ser Glu Ser Ala Leu Asn Glu Glu Trp
1105                1110                1115                1120
His Ser Asp Asn Ser Asp Gly Glu Ile Ala Ser Glu Cys Glu Cys Asp
                1125                1130                1135
Ser Val Phe Asn His Leu Glu Glu Leu Arg Leu His Leu Glu Gln Glu
            1140                1145                1150
Met Gly Phe Glu Lys Phe Phe Glu Val Tyr Glu Lys Ile Lys Ala Ile
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His Glu Asp Glu Asp Glu Asn Ile Glu Ile Cys Ser Lys Ile Val Gln
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Asn Ile Leu Gly Asn Glu His Gln His Leu Tyr Ala Lys Ile Leu His
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<212> DNA
<213> homo sapiens

<400> 5

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<212> PRT
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Lys Arg Asn Pro Arg Asp Arg Pro Ser Val Asn Ser Ile Leu Glu Lys
        35                  40                  45
Gly Phe Ile Ala Lys Arg Ile Glu Lys Phe Leu Ser Pro Gln Leu Ile
    50                  55                  60
Ala Glu Glu Phe Cys Leu Lys Thr Phe Ser Lys Phe Gly Ser Gln Pro
65                  70                  75                  80
Ile Pro Ala Lys Arg Pro Ala Ser Gly Gln Asn Ser Ile Ser Val Met
                85                  90                  95
Pro Ala Gln Lys Ile Thr Lys Pro Ala Ala Lys Tyr Gly Ile Pro Leu
            100                 105                 110
Ala Tyr Lys Lys Tyr Gly Asp Lys Lys Leu His Glu Lys Lys Pro Leu
        115                 120                 125
Gln Lys His Lys Gln Ala His Gln Thr Pro Glu Lys Arg Val Asn Thr
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Gly Glu Glu Arg Arg Lys Ile Ser Glu Glu Ala Ala Arg Lys Arg Arg
145                 150                 155                 160
Leu Glu Phe Ile Glu Lys Glu Lys Lys Gln Lys Asp Gln Ile Ile Ser
                165                 170                 175
Leu Met Lys Ala Glu Gln Met Lys Arg Gln Glu Lys Glu Arg Leu Glu
            180                 185                 190
Arg Ile Asn Arg Ala Arg Glu Gln Gly Trp Arg Asn Val Leu Ser Ala
        195                 200                 205
Gly Gly Ser Gly Glu Val Lys Ala Pro Phe Leu Gly Ser Gly Gly Thr
    210                 215                 220
Ile Ala Pro Ser Ser Phe Ser Ser Arg Gly Gln Tyr Glu His Tyr His
225                 230                 235                 240
Ala Ile Phe Asp Gln Met Gln Gln Gln Arg Ala Glu Asp Asn Glu Ala
                245                 250                 255
Lys Trp Lys Arg Glu Ile Tyr Gly Arg Gly Leu Pro Glu Arg Gln Lys
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Gly Gln Leu Ala Val Glu Arg Ala Lys Gln Val Glu Glu Phe Leu Gln
        275                 280                 285
Arg Lys Arg Glu Ala Met Gln Asn Lys Ala Arg Ala Glu Gly His Met
    290                 295                 300
Val Tyr Leu Ala Arg Leu Arg Gln Ile Arg Leu Gln Asn Phe Asn Glu
305                 310                 315                 320
Arg Gln Gln Ile Lys Ala Lys Leu Arg Gly Glu Lys Lys Glu Ala Asn
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His Ser Glu Gly Gln Glu Gly Ser Glu Glu Ala Asp Met Arg Arg Lys
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Lys Ile Glu Ser Leu Lys Ala His Ala Asn Ala Arg Ala Ala Val Leu
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    370                 375                 380
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385                 390                 395                 400
Val Ser Pro Pro Leu Gly Gln His Glu Thr Gly Gly Ser Pro Ser Lys
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Gly Val Asp Ser Ser Leu Thr Asp Thr Arg Glu Thr Ser Glu Glu Met
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Leu Ser Asp Thr Phe Glu Ile Asn Val His Glu Asp Ala Lys Glu His
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Glu Lys Glu Lys Ser Val Ser Ser Asp Arg Lys Lys Trp Glu Ala Gly
            500                 505                 510
Gly Gln Leu Val Ile Pro Leu Asp Glu Leu Thr Leu Asp Thr Ser Phe
        515                 520                 525
Ser Thr Thr Glu Arg His Thr Val Gly Glu Val Ile Lys Leu Gly Pro
    530                 535                 540
Asn Gly Ser Pro Arg Arg Ala Trp Gly Lys Ser Pro Thr Asp Ser Val
545                 550                 555                 560
Leu Lys Ile Leu Gly Glu Ala Glu Leu Gln Leu Gln Thr Glu Leu Leu
                565                 570                 575
Glu Asn Thr Thr Ile Arg Ser Glu Ile Ser Pro Glu Gly Glu Lys Tyr
            580                 585                 590
Lys Pro Leu Ile Thr Gly Glu Lys Lys Val Gln Cys Ile Ser His Glu
        595                 600                 605
Ile Asn Pro Ser Ala Ile Val Asp Ser Pro Val Glu Thr Lys Ser Pro
    610                 615                 620
Glu Phe Ser Glu Ala Ser Pro Gln Met Ser Leu Lys Leu Glu Gly Asn
625                 630                 635                 640
Leu Glu Glu Pro Asp Asp Leu Glu Thr Glu Ile Leu Gln Glu Pro Ser
                645                 650                 655
Gly Thr Asn Lys Asp Glu Ser Leu Pro Cys Thr Ile Thr Asp Val Trp
            660                 665                 670
Ile Ser Glu Glu Lys Glu Thr Lys Glu Thr Gln Ser Ala Asp Arg Ile
        675                 680                 685
Thr Ile Gln Glu Asn Glu Val Ser Glu Asp Gly Val Ser Ser Thr Val
    690                 695                 700
Asp Gln Leu Ser Asp Ile His Ile Glu Pro Gly Thr Asn Asp Ser Gln
705                 710                 715                 720
His Ser Lys Cys Asp Val Asp Lys Ser Val Gln Pro Glu Pro Phe Phe
                725                 730                 735
His Lys Val Val His Ser Glu His Leu Asn Leu Val Pro Gln Val Gln
            740                 745                 750
Ser Val Gln Cys Ser Pro Glu Glu Ser Phe Ala Phe Arg Ser His Ser
        755                 760                 765
His Leu Pro Pro Lys Asn Lys Asn Lys Asn Ser Leu Leu Ile Gly Leu
    770                 775                 780
Ser Thr Gly Leu Phe Asp Ala Asn Asn Pro Lys Met Leu Arg Thr Cys
785                 790                 795                 800
Ser Leu Pro Asp Leu Ser Lys Leu Phe Arg Thr Leu Met Asp Val Pro
                805                 810                 815
Thr Val Gly Asp Val Arg Gln Asp Asn Leu Glu Ile Asp Glu Ile Lys
            820                 825                 830
Asp Glu Asn Ile Lys Glu Gly Pro Ser Asp Ser Glu Asp Ile Val Phe
        835                 840                 845
Glu Glu Thr Asp Thr Asp Leu Gln Glu Leu Gln Ala Ser Met Glu Gln
    850                 855                 860
Leu Leu Arg Glu Gln Pro Gly Glu Glu Tyr Ser Glu Glu Glu Glu Ser
865                 870                 875                 880
Val Leu Lys Asn Ser Asp Val Glu Pro Thr Ala Asn Gly Thr Asp Val
```

```
                885                 890                 895
Ala Asp Glu Asp Asp Asn Pro Ser Ser Glu Ser Ala Leu Asn Glu Glu
            900                 905                 910
Trp His Ser Asp Asn Ser Asp Gly Glu Ile Ala Ser Glu Cys Glu Cys
        915                 920                 925
Asp Ser Val Phe Asn His Leu Glu Glu Leu Arg Leu His Leu Glu Gln
    930                 935                 940
Glu Met Gly Phe Glu Lys Phe Phe Glu Val Tyr Glu Lys Ile Lys Ala
945                 950                 955                 960
Ile His Glu Asp Glu Asp Glu Asn Ile Glu Ile Cys Ser Lys Ile Val
                965                 970                 975
Gln Asn Ile Leu Gly Asn Glu His Gln His Leu Tyr Ala Lys Ile Leu
            980                 985                 990
His Leu Val Met Ala Asp Gly Ala Tyr Gln Glu Asp Asn Asp Glu
        995                 1000                1005
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<210> 7
<211> 891
<212> DNA
<213> homo sapiens

<400> 7

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ctgccagccc agctgcagcc acatgtggat agccaggaag acctgacctt cctctgggat     120
atgtttggtg aaaaaagcct gcattcattg gtaaagattc atgaaaaact acactactat     180
gagaagcaga gtccggtgcc cattctccat ggtgcggcgg ccttggccga tgatctggcc     240
gaagagcttc agaacaagcc attaaacagt gagatcagag agctgttgaa actactgtca     300
aaacccaatg tgaaggcttt gctctctgta catgatactg tggctcagaa gaattacgac     360
ccagtgttgc ctcctatgcc tgaagatatt gacgatgagg aagactcagt aaaaataatc     420
cgtctggtca aaaatagaga accactggga gctaccatta agaaggatga acagaccggg     480
gcgatcattg tggccagaat catgagagga ggagctgcag atagaagtgg tcttattcat     540
gttggtgatg aacttaggga agtcaacggg ataccagtgg aggataaaag gcctgaggaa     600
ataatacaga ttttggctca gtctcaggga gcaattacat ttaagattat acccggcagc     660
aaagaggaga caccatcaaa agaaggcaag atgtttatca aagccctctt tgactataat     720
cctaatgagg ataaggcaat tccatgtaag gaagctgggc tttctttcaa aaagggagat     780
attcttcaga ttatgagcca agatgatgca acttggtggc aagcgaaaca cgaagctgat     840
gccaacccca gggcaggctt gatcccctca aagcatttcc aggaaaggtg a               891
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<210> 8
<211> 296
<212> PRT
<213> homo sapiens

<400> 8

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Met Pro Ala Leu Ser Thr Gly Ser Gly Ser Asp Thr Gly Leu Tyr Glu
 1               5                  10                  15
Leu Leu Ala Ala Leu Pro Ala Gln Leu Gln Pro His Val Asp Ser Gln
            20                  25                  30
Glu Asp Leu Thr Phe Leu Trp Asp Met Phe Gly Glu Lys Ser Leu His
        35                  40                  45
Ser Leu Val Lys Ile His Glu Lys Leu His Tyr Tyr Glu Lys Gln Ser
    50                  55                  60
Pro Val Pro Ile Leu His Gly Ala Ala Ala Leu Ala Asp Asp Leu Ala
65                  70                  75                  80
Glu Glu Leu Gln Asn Lys Pro Leu Asn Ser Glu Ile Arg Glu Leu Leu
```

```
                85                  90                  95
Lys Leu Leu Ser Lys Pro Asn Val Lys Ala Leu Leu Ser Val His Asp
            100                 105                 110
Thr Val Ala Gln Lys Asn Tyr Asp Pro Val Leu Pro Pro Met Pro Glu
        115                 120                 125
Asp Ile Asp Asp Glu Glu Asp Ser Val Lys Ile Ile Arg Leu Val Lys
    130                 135                 140
Asn Arg Glu Pro Leu Gly Ala Thr Ile Lys Lys Asp Glu Gln Thr Gly
145                 150                 155                 160
Ala Ile Ile Val Ala Arg Ile Met Arg Gly Gly Ala Ala Asp Arg Ser
                165                 170                 175
Gly Leu Ile His Val Gly Asp Glu Leu Arg Glu Val Asn Gly Ile Pro
            180                 185                 190
Val Glu Asp Lys Arg Pro Glu Glu Ile Ile Gln Ile Leu Ala Gln Ser
        195                 200                 205
Gln Gly Ala Ile Thr Phe Lys Ile Ile Pro Gly Ser Lys Glu Glu Thr
    210                 215                 220
Pro Ser Lys Glu Gly Lys Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
225                 230                 235                 240
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
                245                 250                 255
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
            260                 265                 270
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
        275                 280                 285
Pro Ser Lys His Phe Gln Glu Arg
    290                 295
```

<210> 9
<211> 219
<212> DNA
<213> homo sapiens

<400> 9
atgaaacttt tcttccagat gtttatcaaa gccctctttg actataatcc taatgaggat 60
aaggcaattc catgtaagga agctgggctt tctttcaaaa agggagatat tcttcagatt 120
atgagccaag atgatgcaac ttggtggcaa gcgaaacacg aagctgatgc caaccccagg 180
gcaggcttga tcccctcaaa gcatttccag gaaaggtga 219

<210> 10
<211> 72
<212> PRT
<213> homo sapiens

<400> 10
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Met Lys Leu Phe Phe Gln Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
 1               5                  10                  15
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
            20                  25                  30
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
        35                  40                  45
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
    50                  55                  60
Pro Ser Lys His Phe Gln Glu Arg
65                  70
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<210> 11
<211> 957
<212> DNA
<213> homo sapiens

<400> 11
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atgtttggtg aaaaaagcct gcattcattg gtaaagattc atgaaaaact acactactat 180
gagaagcaga gtccggtgcc cattctccat ggtgcggcgg ccttggccga tgatctggcc 240
gaagagcttc agaacaagcc attaaacagt gagatcagag agctgttgaa actactgtca 300
aaacccaatg tgaaggcttt gctctctgta catgatactg tggctcagaa gaattacgac 360
ccagtgttgc ctcctatgcc tgaagatatt gacgatgagg aagactcagt aaaaataatc 420
cgtctggtca aaaatagaga accactggga gctaccatta agaaggatga acagaccggg 480
gcgatcattg tggccagaat catgagagga ggagctgcag atagaagtgg tcttattcat 540
gttggtgatg aacttaggga agtcaacggg ataccagtgg aggataaaag gcctgaggaa 600
ataatacaga ttttggctca gtctcaggga gcaattacat ttaagattat acccggcagc 660
aaagaggaga caccatcaaa agaaggcaag atgtttatca aagccctctt tgactataat 720
cctaatgagg ataaggcaat tccatgtaag gaagctgggc tttctttcaa aaagggagat 780
attcttcaga ttatgagcca agatgatgca acttggtggc aagcgaaaca cgaagctgat 840
gccaacccca gggcaggctt gatcccctca aagcatttcc aggaaaggag attggctttg 900
agacgaccag aaatattggt tcagcccctg aaagtttcca acaggaaatc atcctaa 957

<210> 12
<211> 318
<212> PRT
<213> homo sapiens

<400> 12
Met Pro Ala Leu Ser Thr Gly Ser Gly Ser Asp Thr Gly Leu Tyr Glu
1 5 10 15
Leu Leu Ala Ala Leu Pro Ala Gln Leu Gln Pro His Val Asp Ser Gln
20 25 30
Glu Asp Leu Thr Phe Leu Trp Asp Met Phe Gly Glu Lys Ser Leu His
35 40 45
Ser Leu Val Lys Ile His Glu Lys Leu His Tyr Tyr Glu Lys Gln Ser
50 55 60
Pro Val Pro Ile Leu His Gly Ala Ala Ala Leu Ala Asp Asp Leu Ala
65 70 75 80
Glu Glu Leu Gln Asn Lys Pro Leu Asn Ser Glu Ile Arg Glu Leu Leu
85 90 95
Lys Leu Leu Ser Lys Pro Asn Val Lys Ala Leu Leu Ser Val His Asp
100 105 110
Thr Val Ala Gln Lys Asn Tyr Asp Pro Val Leu Pro Pro Met Pro Glu
115 120 125
Asp Ile Asp Asp Glu Glu Asp Ser Val Lys Ile Ile Arg Leu Val Lys
130 135 140
Asn Arg Glu Pro Leu Gly Ala Thr Ile Lys Lys Asp Glu Gln Thr Gly
145 150 155 160
Ala Ile Ile Val Ala Arg Ile Met Arg Gly Gly Ala Ala Asp Arg Ser
165 170 175
Gly Leu Ile His Val Gly Asp Glu Leu Arg Glu Val Asn Gly Ile Pro
180 185 190
Val Glu Asp Lys Arg Pro Glu Glu Ile Ile Gln Ile Leu Ala Gln Ser
195 200 205
Gln Gly Ala Ile Thr Phe Lys Ile Ile Pro Gly Ser Lys Glu Glu Thr

```
    210                 215                 220
Pro Ser Lys Glu Gly Lys Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
225                 230                 235                 240
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
                245                 250                 255
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
            260                 265                 270
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
        275                 280                 285
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
    290                 295                 300
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser
305                 310                 315
```

<210> 13
<211> 285
<212> DNA
<213> homo sapiens

<400> 13
atgaaacttt tcttccagat gtttatcaaa gccctctttg actataatcc taatgaggat 60
aaggcaattc catgtaagga agctgggctt tctttcaaaa agggagatat tcttcagatt 120
atgagccaag atgatgcaac ttggtggcaa gcgaaacacg aagctgatgc caacccccagg 180
gcaggcttga tcccctcaaa gcatttccag gaaaggagat tggctttgag acgaccagaa 240
atattggttc agcccctgaa agtttccaac aggaaatcat cctaa 285

<210> 14
<211> 94
<212> PRT
<213> homo sapiens

<400> 14
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Met Lys Leu Phe Phe Gln Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
 1               5                  10                  15
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
            20                  25                  30
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
        35                  40                  45
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
    50                  55                  60
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
65                  70                  75                  80
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser
                85                  90
```

<210> 15
<211> 327
<212> DNA
<213> homo sapiens

<400> 15
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cgaaagctgc tgatcagtga cacccagcac tatggcgtga cagtgcccca taccaccaga 120
gcaagaagaa gccaggagag tgatggtgtt gaatacattt tcatttccaa gcatttgttt 180
gagacagatg tacaaaataa caagtttatt gaatatggag aatataaaaa caactactac 240
ggcacaagta tagactcagt tcggtctgtc cttgctaaaa acaaagtttg tttgttggat 300

gttcagcctc atgtaagtaa acaatga 327

<210> 16
<211> 108
<212> PRT
<213> homo sapiens

<400> 16
Met Cys Cys Pro Lys Thr Ala Cys Arg Gly Pro Val Gly Val Gly Leu
1 5 10 15
Asn Glu Leu Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly
20 25 30
Val Thr Val Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp
35 40 45
Gly Val Glu Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val
50 55 60
Gln Asn Asn Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr
65 70 75 80
Gly Thr Ser Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val
85 90 95
Cys Leu Leu Asp Val Gln Pro His Val Ser Lys Gln
100 105

<210> 17
<211> 1128
<212> DNA
<213> homo sapiens

<400> 17
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ctgccagccc agctgcagcc acatgtggat agccaggaag acctgacctt cctctgggat 120
atgtttggtg aaaaaagcct gcattcattg gtaaagattc atgaaaaact acactactat 180
gagaagcaga gtccggtgcc cattctccat ggtgcggcgg ccttggccga tgatctggcc 240
gaagagcttc agaacaagcc attaaacagt gagatcagag agctgttgaa actactgtca 300
aaacccaatg tgaaggcttt gctctctgta catgatactg tggctcagaa gaattacgac 360
ccagtgttgc ctcctatgcc tgaagatatt gacgatgagg aagactcagt aaaaataatc 420
cgtctggtca aaaatagaga accactggga gctaccatta agaaggatga acagaccggg 480
gcgatcattg tggccagaat catgagagga ggagctgcag atagaagtgg tcttattcat 540
gttggtgatg aacttaggga agtcaacggg ataccagtgg aggataaaag gcctgaggaa 600
ataatacaga ttttggctca gtctcaggga gcaattacat ttaagattat acccggcagc 660
aaagaggaga caccatcaaa agaaggcaag atgtttatca aagccctctt tgactataat 720
cctaatgagg ataaggcaat tccatgtaag gaagctgggc tttctttcaa aaagggagat 780
attcttcaga ttatgagcca agatgatgca acttggtggc aagcgaaaca cgaagctgat 840
gccaacccca gggcaggctt gatcccctca aagcatttcc aggaaaggag attggctttg 900
agacgaccag aaatattggt tcagcccctg aaagtttcca acaggaaatc atctggtttt 960
agaagaagtt ttcgtcttag tagaaaagat aagaaaacaa ataaatccat gtatgaatgc 1020
aagaagagtg atcagtacga cacagctgac gtacccacat acgaagaagt gacaccgtat 1080
cggcgacaaa ctaatgaaaa atacagactc gttgtcttgg ttgcttga 1128

<210> 18
<211> 375
<212> PRT
<213> homo sapiens

<400> 18
Met Pro Ala Leu Ser Thr Gly Ser Gly Ser Asp Thr Gly Leu Tyr Glu

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 1               5                  10                  15
Leu Leu Ala Ala Leu Pro Ala Gln Leu Gln Pro His Val Asp Ser Gln
            20                  25                  30
Glu Asp Leu Thr Phe Leu Trp Asp Met Phe Gly Glu Lys Ser Leu His
        35                  40                  45
Ser Leu Val Lys Ile His Glu Lys Leu His Tyr Tyr Glu Lys Gln Ser
    50                  55                  60
Pro Val Pro Ile Leu His Gly Ala Ala Ala Leu Ala Asp Asp Leu Ala
65                  70                  75                  80
Glu Glu Leu Gln Asn Lys Pro Leu Asn Ser Glu Ile Arg Glu Leu Leu
                85                  90                  95
Lys Leu Leu Ser Lys Pro Asn Val Lys Ala Leu Leu Ser Val His Asp
            100                 105                 110
Thr Val Ala Gln Lys Asn Tyr Asp Pro Val Leu Pro Pro Met Pro Glu
        115                 120                 125
Asp Ile Asp Asp Glu Glu Asp Ser Val Lys Ile Ile Arg Leu Val Lys
    130                 135                 140
Asn Arg Glu Pro Leu Gly Ala Thr Ile Lys Lys Asp Glu Gln Thr Gly
145                 150                 155                 160
Ala Ile Ile Val Ala Arg Ile Met Arg Gly Gly Ala Ala Asp Arg Ser
                165                 170                 175
Gly Leu Ile His Val Gly Asp Glu Leu Arg Glu Val Asn Gly Ile Pro
            180                 185                 190
Val Glu Asp Lys Arg Pro Glu Glu Ile Ile Gln Ile Leu Ala Gln Ser
        195                 200                 205
Gln Gly Ala Ile Thr Phe Lys Ile Ile Pro Gly Ser Lys Glu Glu Thr
    210                 215                 220
Pro Ser Lys Glu Gly Lys Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
225                 230                 235                 240
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
                245                 250                 255
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
            260                 265                 270
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
        275                 280                 285
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
    290                 295                 300
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser Gly Phe
305                 310                 315                 320
Arg Arg Ser Phe Arg Leu Ser Arg Lys Asp Lys Lys Thr Asn Lys Ser
                325                 330                 335
Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
            340                 345                 350
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
        355                 360                 365
Arg Leu Val Val Leu Val Ala
    370                 375
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<210> 19
<211> 414
<212> DNA
<213> homo sapiens

<400> 19
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gtgacaccgt atcggcgaca aactaatgaa aaatacagac tcgttgtctt ggttggtccc 120

gtgggagtag ggctgaatga actgaaacga aagctgctga tcagtgacac ccagcactat 180
ggcgtgacag tgccccatac caccagagca agaagaagcc aggagagtga tggtgttgaa 240
tacattttca tttccaagca tttgtttgag acagatgtac aaaataacaa gtttattgaa 300
tatggagaat ataaaaacaa ctactacggc acaagtatag actcagttcg gtctgtcctt 360
gctaaaaaca aagtttgttt gttggatgtt cagcctcatg taagtaaaca atga 414

<210> 20
<211> 137
<212> PRT
<213> homo sapiens

<400> 20
Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
1 5 10 15
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
20 25 30
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
35 40 45
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
50 55 60
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
65 70 75 80
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
85 90 95
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
100 105 110
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
115 120 125
Asp Val Gln Pro His Val Ser Lys Gln
130 135

<210> 21
<211> 1422
<212> DNA
<213> homo sapiens

<400> 21
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ctgccagccc agctgcagcc acatgtggat agccaggaag acctgacctt cctctgggat 120
atgtttggtg aaaaaagcct gcattcattg gtaaagattc atgaaaaact acactactat 180
gagaagcaga gtccggtgcc cattctccat ggtgcggcgg ccttggccga tgatctggcc 240
gaagagcttc agaacaagcc attaaacagt gagatcagag agctgttgaa actactgtca 300
aaacccaatg tgaaggcttt gctctctgta catgatactg tggctcagaa gaattacgac 360
ccagtgttgc ctcctatgcc tgaagatatt gacgatgagg aagactcagt aaaaataatc 420
cgtctggtca aaaatagaga accactggga gctaccatta agaaggatga acagaccggg 480
gcgatcattg tggccagaat catgagagga ggagctgcag atagaagtgg tcttattcat 540
gttggtgatg aacttaggga agtcaacggg ataccagtgg aggataaaag gcctgaggaa 600
ataatacaga ttttggctca gtctcaggga gcaattacat ttaagattat acccggcagc 660
aaagaggaga caccatcaaa agaaggcaag atgtttatca aagccctctt tgactataat 720
cctaatgagg ataaggcaat tccatgtaag gaagctgggc tttctttcaa aaagggagat 780
attcttcaga ttatgagcca agatgatgca acttggtggc aagcgaaaca cgaagctgat 840
gccaacccca gggcaggctt gatcccctca aagcatttcc aggaaaggag attggctttg 900
agacgaccag aaatattggt tcagcccctg aaagtttcca acaggaaatc atctggtttt 960
agaagaagtt ttcgtcttag tagaaaagat aagaaaacaa ataaatccat gtatgaatgc 1020
aagaagagtg atcagtacga cacagctgac gtacccacat acgaagaagt gacaccgtat 1080
cggcgacaaa ctaatgaaaa atacagactc gttgtcttgg ttggtcccgt gggagtaggg 1140

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Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
        355                 360                 365
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
    370                 375                 380
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
385                 390                 395                 400
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
                405                 410                 415
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
            420                 425                 430
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
        435                 440                 445
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
    450                 455                 460
Asp Val Gln Pro His Val Ser Lys Gln
465                 470
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<210> 23
<211> 750
<212> DNA
<213> homo sapiens

<400> 23

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aaggcaattc catgtaagga agctgggctt tctttcaaaa agggagatat tcttcagatt     120
atgagccaag atgatgcaac ttggtggcaa gcgaaacacg aagctgatgc caaccccagg     180
gcaggcttga tcccctcaaa gcatttccag gaaaggagat tggctttgag acgaccagaa     240
atattggttc agcccctgaa agtttccaac aggaaatcat ctggttttag aagaagtttt     300
cgtcttagta gaaaagataa gaaaacaaat aaatccatgt atgaatgcaa gaagagtgat     360
cagtacgaca cagctgacgt acccacatac gaagaagtga caccgtatcg gcgacaaact     420
aatgaaaaat acagactcgt tgtcttggtt ggtcccgtgg gagtagggct gaatgaactg     480
aaacgaaagc tgctgatcag tgacacccag cactatggcg tgacagtgcc ccataccacc     540
agagcaagaa gaagccagga gagtgatggt gttgaataca ttttcatttc caagcatttg     600
tttgagacag atgtacaaaa taacaagttt attgaatatg gagaatataa aaacaactac     660
tacggcacaa gtatagactc agttcggtct gtccttgcta aaaacaaagt ttgtttgttg     720
gatgttcagc ctcatgtaag taaacaatga                                      750
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<210> 24
<211> 249
<212> PRT
<213> homo sapiens

<400> 24

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Met Lys Leu Phe Phe Gln Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
 1               5                  10                  15
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
            20                  25                  30
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
        35                  40                  45
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
    50                  55                  60
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
65                  70                  75                  80
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser Gly Phe
                85                  90                  95
Arg Arg Ser Phe Arg Leu Ser Arg Lys Asp Lys Lys Thr Asn Lys Ser
```

```
            100                 105                 110
Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
        115                 120                 125
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
    130                 135                 140
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
145                 150                 155                 160
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
                165                 170                 175
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
            180                 185                 190
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
        195                 200                 205
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
    210                 215                 220
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
225                 230                 235                 240
Asp Val Gln Pro His Val Ser Lys Gln
                245
```

<210> 25
<211> 468
<212> DNA
<213> homo sapiens

<400> 25

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atgtgctgcc caaagactgc ttgcagaggt cccgtgggag tagggctgaa tgaactgaaa      60
cgaaagctgc tgatcagtga cacccagcac tatggcgtga cagtgcccca taccaccaga     120
gcaagaagaa gccaggagag tgatggtgtt gaatacattt tcatttccaa gcatttgttt     180
gagacagatg tacaaaataa caagtttatt gaatatggag aatataaaaa caactactac     240
ggcacaagta tagactcagt tcggtctgtc cttgctaaaa acaaagtttg tttgttggat     300
gttcagcctc atacagtgaa gcatttaagg acactagaat ttaagcccta tgtgatattt     360
ataaagcctc catcaataga gcgtttgaga gaaacaagaa aaaatgcaaa gattatttca     420
agcagagatg accaaggtgc tgcaaaaccc ttcacacaag gagaatag                  468
```

<210> 26
<211> 155
<212> PRT
<213> homo sapiens

<400> 26

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Met Cys Cys Pro Lys Thr Ala Cys Arg Gly Pro Val Gly Val Gly Leu
 1               5                  10                  15
Asn Glu Leu Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly
            20                  25                  30
Val Thr Val Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp
        35                  40                  45
Gly Val Glu Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val
    50                  55                  60
Gln Asn Asn Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr
65                  70                  75                  80
Gly Thr Ser Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val
                85                  90                  95
Cys Leu Leu Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu
            100                 105                 110
Glu Phe Lys Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg
```

```
        115                 120                 125
Leu Arg Glu Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp
    130                 135                 140
Gln Gly Ala Ala Lys Pro Phe Thr Gln Gly Glu
145                 150                 155
```

<210> 27
<211> 555
<212> DNA
<213> homo sapiens

<400> 27

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atgtatgaat gcaagaagag tgatcagtac gacacagctg acgtacccac atacgaagaa      60
gtgacaccgt atcggcgaca aactaatgaa aaatacagac tcgttgtctt ggttggtccc     120
gtgggagtag ggctgaatga actgaaacga aagctgctga tcagtgacac ccagcactat     180
ggcgtgacag tgccccatac caccagagca agaagaagcc aggagagtga tggtgttgaa     240
tacattttca tttccaagca tttgtttgag acagatgtac aaaataacaa gtttattgaa     300
tatggagaat ataaaaacaa ctactacggc acaagtatag actcagttcg gtctgtcctt     360
gctaaaaaca aagtttgttt gttggatgtt cagcctcata cagtgaagca tttaaggaca     420
ctagaattta agccctatgt gatatttata aagcctccat caatagagcg tttgagagaa     480
acaagaaaaa atgcaaagat tatttcaagc agagatgacc aaggtgctgc aaaacccttc     540
acacaaggag aatag                                                      555
```

<210> 28
<211> 184
<212> PRT
<213> homo sapiens

<400> 28

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Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
 1               5                  10                  15
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
            20                  25                  30
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
        35                  40                  45
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
    50                  55                  60
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
65                  70                  75                  80
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
                85                  90                  95
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
            100                 105                 110
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
        115                 120                 125
Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu Glu Phe Lys
    130                 135                 140
Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg Leu Arg Glu
145                 150                 155                 160
Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp Gln Gly Ala
                165                 170                 175
Ala Lys Pro Phe Thr Gln Gly Glu
            180
```

<210> 29
<211> 1563

<212> DNA
<213> homo sapiens

<400> 29
atgccagctt tgtcaacggg atctgggagt gacactggtc tgtatgagct gttggctgct 60
ctgccagccc agctgcagcc acatgtggat agccaggaag acctgacctt cctctgggat 120
atgtttggtg aaaaaagcct gcattcattg gtaaagattc atgaaaaact acactactat 180
gagaagcaga gtccggtgcc cattctccat ggtgcggcgg ccttggccga tgatctggcc 240
gaagagcttc agaacaagcc attaaacagt gagatcagag agctgttgaa actactgtca 300
aaacccaatg tgaaggcttt gctctctgta catgatactg tggctcagaa gaattacgac 360
ccagtgttgc ctcctatgcc tgaagatatt gacgatgagg aagactcagt aaaaataatc 420
cgtctggtca aaaatagaga accactggga gctaccatta agaaggatga acagaccggg 480
gcgatcattg tggccagaat catgagagga ggagctgcag atagaagtgg tcttattcat 540
gttggtgatg aacttaggga agtcaacggg ataccagtgg aggataaaag gcctgaggaa 600
ataatacaga ttttggctca gtctcaggga gcaattacat ttaagattat acccggcagc 660
aaagaggaga caccatcaaa agaaggcaag atgtttatca aagccctctt tgactataat 720
cctaatgagg ataaggcaat tccatgtaag gaagctgggc tttctttcaa aaagggagat 780
attcttcaga ttatgagcca agatgatgca acttggtggc aagcgaaaca cgaagctgat 840
gccaacccca gggcaggctt gatcccctca aagcatttcc aggaaaggag attggctttg 900
agacgaccag aaatattggt tcagcccctg aaagtttcca acaggaaatc atctggtttt 960
agaagaagtt ttcgtcttag tagaaaagat aagaaaacaa ataaatccat gtatgaatgc 1020
aagaagagtg atcagtacga cacagctgac gtacccacat acgaagaagt gacaccgtat 1080
cggcgacaaa ctaatgaaaa atacagactc gttgtcttgg ttggtcccgt gggagtaggg 1140
ctgaatgaac tgaaacgaaa gctgctgatc agtgacaccc agcactatgg cgtgacagtg 1200
ccccatacca ccagagcaag aagaagccag gagagtgatg gtgttgaata cattttcatt 1260
tccaagcatt tgtttgagac agatgtacaa aataacaagt ttattgaata tggagaatat 1320
aaaaacaact actacggcac aagtatagac tcagttcggt ctgtccttgc taaaaacaaa 1380
gtttgtttgt tggatgttca gcctcataca gtgaagcatt taaggacact agaatttaag 1440
ccctatgtga tatttataaa gcctccatca atagagcgtt tgagagaaac aagaaaaaat 1500
gcaaagatta tttcaagcag agatgaccaa ggtgctgcaa aacccttcac acaaggagaa 1560
tag 1563

<210> 30
<211> 520
<212> PRT
<213> homo sapiens

<400> 30
Met Pro Ala Leu Ser Thr Gly Ser Gly Ser Asp Thr Gly Leu Tyr Glu
1 5 10 15
Leu Leu Ala Ala Leu Pro Ala Gln Leu Gln Pro His Val Asp Ser Gln
20 25 30
Glu Asp Leu Thr Phe Leu Trp Asp Met Phe Gly Glu Lys Ser Leu His
35 40 45
Ser Leu Val Lys Ile His Glu Lys Leu His Tyr Tyr Glu Lys Gln Ser
50 55 60
Pro Val Pro Ile Leu His Gly Ala Ala Ala Leu Ala Asp Asp Leu Ala
65 70 75 80
Glu Glu Leu Gln Asn Lys Pro Leu Asn Ser Glu Ile Arg Glu Leu Leu
85 90 95
Lys Leu Leu Ser Lys Pro Asn Val Lys Ala Leu Leu Ser Val His Asp
100 105 110
Thr Val Ala Gln Lys Asn Tyr Asp Pro Val Leu Pro Pro Met Pro Glu
115 120 125
Asp Ile Asp Asp Glu Glu Asp Ser Val Lys Ile Ile Arg Leu Val Lys
130 135 140

```
Asn Arg Glu Pro Leu Gly Ala Thr Ile Lys Lys Asp Glu Gln Thr Gly
145                 150                 155                 160
Ala Ile Ile Val Ala Arg Ile Met Arg Gly Gly Ala Ala Asp Arg Ser
                165                 170                 175
Gly Leu Ile His Val Gly Asp Glu Leu Arg Glu Val Asn Gly Ile Pro
            180                 185                 190
Val Glu Asp Lys Arg Pro Glu Glu Ile Ile Gln Ile Leu Ala Gln Ser
        195                 200                 205
Gln Gly Ala Ile Thr Phe Lys Ile Ile Pro Gly Ser Lys Glu Glu Thr
    210                 215                 220
Pro Ser Lys Glu Gly Lys Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
225                 230                 235                 240
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
                245                 250                 255
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
            260                 265                 270
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
        275                 280                 285
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
    290                 295                 300
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser Gly Phe
305                 310                 315                 320
Arg Arg Ser Phe Arg Leu Ser Arg Lys Asp Lys Lys Thr Asn Lys Ser
                325                 330                 335
Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
            340                 345                 350
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
        355                 360                 365
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
    370                 375                 380
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
385                 390                 395                 400
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
                405                 410                 415
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
            420                 425                 430
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
        435                 440                 445
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
    450                 455                 460
Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu Glu Phe Lys
465                 470                 475                 480
Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg Leu Arg Glu
                485                 490                 495
Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp Gln Gly Ala
            500                 505                 510
Ala Lys Pro Phe Thr Gln Gly Glu
        515                 520
```

<210> 31
<211> 891
<212> DNA
<213> homo sapiens

<400> 31
atgaaacttt tcttccagat gtttatcaaa gccctctttg actataatcc taatgaggat 60

aaggcaattc catgtaagga agctgggctt tctttcaaaa agggagatat tcttcagatt 120
atgagccaag atgatgcaac ttggtggcaa gcgaaacacg aagctgatgc caaccccagg 180
gcaggcttga tcccctcaaa gcatttccag gaaaggagat tggctttgag acgaccagaa 240
atattggttc agcccctgaa agtttccaac aggaaatcat ctggttttag aagaagtttt 300
cgtcttagta gaaaagataa gaaaacaaat aaatccatgt atgaatgcaa gaagagtgat 360
cagtacgaca cagctgacgt acccacatac gaagaagtga caccgtatcg gcgacaaact 420
aatgaaaaat acagactcgt tgtcttggtt ggtcccgtgg gagtagggct gaatgaactg 480
aaacgaaagc tgctgatcag tgacacccag cactatggcg tgacagtgcc ccataccacc 540
agagcaagaa gaagccagga gagtgatggt gttgaataca ttttcatttc caagcatttg 600
tttgagacag atgtacaaaa taacaagttt attgaatatg gagaatataa aaacaactac 660
tacggcacaa gtatagactc agttcggtct gtccttgcta aaaacaaagt ttgtttgttg 720
gatgttcagc ctcatacagt gaagcattta aggacactag aatttaagcc ctatgtgata 780
tttataaagc ctccatcaat agagcgtttg agagaaacaa gaaaaaatgc aaagattatt 840
tcaagcagag atgaccaagg tgctgcaaaa cccttcacac aaggagaata g 891

<210> 32
<211> 296
<212> PRT
<213> homo sapiens

<400> 32
Met Lys Leu Phe Phe Gln Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
1 5 10 15
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
20 25 30
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
35 40 45
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
50 55 60
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
65 70 75 80
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser Gly Phe
85 90 95
Arg Arg Ser Phe Arg Leu Ser Arg Lys Asp Lys Lys Thr Asn Lys Ser
100 105 110
Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
115 120 125
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
130 135 140
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
145 150 155 160
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
165 170 175
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
180 185 190
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
195 200 205
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
210 215 220
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
225 230 235 240
Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu Glu Phe Lys
245 250 255
Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg Leu Arg Glu
260 265 270
Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp Gln Gly Ala

```
       275                 280                 285
Ala Lys Pro Phe Thr Gln Gly Glu
    290                 295

<210> 33
<211> 585
<212> DNA
<213> homo sapiens

<400> 33
atgtgctgcc caaagactgc ttgcagaggt cccgtgggag tagggctgaa tgaactgaaa      60
cgaaagctgc tgatcagtga cacccagcac tatggcgtga cagtgcccca taccaccaga     120
gcaagaagaa gccaggagag tgatggtgtt gaatacattt tcatttccaa gcatttgttt     180
gagacagatg tacaaaataa caagtttatt gaatatggag aatataaaaa caactactac     240
ggcacaagta tagactcagt tcggtctgtc cttgctaaaa acaaagtttg tttgttggat     300
gttcagcctc atacagtgaa gcatttaagg acactagaat ttaagcccta tgtgatattt     360
ataaagcctc catcaataga gcgtttgaga gaaacaagaa aaaatgcaaa gattatttca     420
agcagagatg accaaggtgc tgcaaaaccc ttcacagaag aagattttca agaaatgatt     480
aaatctgcac agataatgga aagtcaatat ggtcatcttt ttgacaaaat tataataaat     540
gatgacctca ctgtggcatt caaaaaaaaa aaaaaaaaaa aaaaa                     585

<210> 34
<211> 195
<212> PRT
<213> homo sapiens

<400> 34
Met Cys Cys Pro Lys Thr Ala Cys Arg Gly Pro Val Gly Val Gly Leu
 1               5                  10                  15
Asn Glu Leu Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly
            20                  25                  30
Val Thr Val Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp
        35                  40                  45
Gly Val Glu Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val
    50                  55                  60
Gln Asn Asn Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr
65                  70                  75                  80
Gly Thr Ser Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val
                85                  90                  95
Cys Leu Leu Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu
            100                 105                 110
Glu Phe Lys Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg
        115                 120                 125
Leu Arg Glu Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp
    130                 135                 140
Gln Gly Ala Ala Lys Pro Phe Thr Glu Glu Asp Phe Gln Glu Met Ile
145                 150                 155                 160
Lys Ser Ala Gln Ile Met Glu Ser Gln Tyr Gly His Leu Phe Asp Lys
                165                 170                 175
Ile Ile Ile Asn Asp Asp Leu Thr Val Ala Phe Lys Lys Lys Lys Lys
            180                 185                 190
Lys Lys Lys
        195

<210> 35
<211> 672
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<212> DNA
<213> homo sapiens

<400> 35
atgtatgaat gcaagaagag tgatcagtac gacacagctg acgtacccac atacgaagaa 60
gtgacaccgt atcggcgaca aactaatgaa aaatacagac tcgttgtctt ggttggtccc 120
gtgggagtag ggctgaatga actgaaacga aagctgctga tcagtgacac ccagcactat 180
ggcgtgacag tgccccatac caccagagca agaagaagcc aggagagtga tggtgttgaa 240
tacattttca tttccaagca tttgtttgag acagatgtac aaaataacaa gtttattgaa 300
tatggagaat ataaaaacaa ctactacggc acaagtatag actcagttcg gtctgtcctt 360
gctaaaaaca aagtttgttt gttggatgtt cagcctcata cagtgaagca tttaaggaca 420
ctagaattta agccctatgt gatatttata aagcctccat caatagagcg tttgagagaa 480
acaagaaaaa atgcaaagat tatttcaagc agagatgacc aaggtgctgc aaaacccttc 540
acagaagaag attttcaaga aatgattaaa tctgcacaga taatggaaag tcaatatggt 600
catcttttg acaaaattat aataaatgat gacctcactg tggcattcaa aaaaaaaaaa 660
aaaaaaaaaa aa 672

<210> 36
<211> 224
<212> PRT
<213> homo sapiens

<400> 36
Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
1 5 10 15
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
20 25 30
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
35 40 45
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
50 55 60
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
65 70 75 80
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
85 90 95
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
100 105 110
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
115 120 125
Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu Glu Phe Lys
130 135 140
Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg Leu Arg Glu
145 150 155 160
Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp Gln Gly Ala
165 170 175
Ala Lys Pro Phe Thr Glu Glu Asp Phe Gln Glu Met Ile Lys Ser Ala
180 185 190
Gln Ile Met Glu Ser Gln Tyr Gly His Leu Phe Asp Lys Ile Ile Ile
195 200 205
Asn Asp Asp Leu Thr Val Ala Phe Lys Lys Lys Lys Lys Lys Lys Lys
210 215 220

<210> 37
<211> 1680
<212> DNA
<213> homo sapiens

<400> 37
atgccagctt tgtcaacggg atctgggagt gacactggtc tgtatgagct gttggctgct 60
ctgccagccc agctgcagcc acatgtggat agccaggaag acctgacctt cctctgggat 120
atgtttggtg aaaaaagcct gcattcattg gtaaagattc atgaaaaact acactactat 180
gagaagcaga gtccggtgcc cattctccat ggtgcggcgg ccttggccga tgatctggcc 240
gaagagcttc agaacaagcc attaaacagt gagatcagag agctgttgaa actactgtca 300
aaacccaatg tgaaggcttt gctctctgta catgatactg tggctcagaa gaattacgac 360
ccagtgttgc ctcctatgcc tgaagatatt gacgatgagg aagactcagt aaaaataatc 420
cgtctggtca aaaatagaga accactggga gctaccatta agaaggatga acagaccggg 480
gcgatcattg tggccagaat catgagagga ggagctgcag atagaagtgg tcttattcat 540
gttggtgatg aacttaggga agtcaacggg ataccagtgg aggataaaag gcctgaggaa 600
ataatacaga ttttggctca gtctcaggga gcaattacat ttaagattat acccggcagc 660
aaagaggaga caccatcaaa agaaggcaag atgtttatca aagccctctt tgactataat 720
cctaatgagg ataaggcaat tccatgtaag gaagctgggc tttctttcaa aaagggagat 780
attcttcaga ttatgagcca agatgatgca acttggtggc aagcgaaaca cgaagctgat 840
gccaacccca gggcaggctt gatcccctca aagcatttcc aggaaaggag attggctttg 900
agacgaccag aaatattggt tcagcccctg aaagtttcca acaggaaatc atctggtttt 960
agaagaagtt ttcgtcttag tagaaaagat aagaaaacaa ataaatccat gtatgaatgc 1020
aagaagagtg atcagtacga cacagctgac gtacccacat acgaagaagt gacaccgtat 1080
cggcgacaaa ctaatgaaaa atacagactc gttgtcttgg ttggtcccgt gggagtaggg 1140
ctgaatgaac tgaaacgaaa gctgctgatc agtgacaccc agcactatgg cgtgacagtg 1200
ccccatacca ccagagcaag aagaagccag gagagtgatg gtgttgaata cattttcatt 1260
tccaagcatt tgtttgagac agatgtacaa aataacaagt ttattgaata tggagaatat 1320
aaaaacaact actacggcac aagtatagac tcagttcggt ctgtccttgc taaaaacaaa 1380
gtttgtttgt tggatgttca gcctcataca gtgaagcatt taaggacact agaatttaag 1440
ccctatgtga tatttataaa gcctccatca atagagcgtt tgagagaaac aagaaaaaat 1500
gcaaagatta tttcaagcag agatgaccaa ggtgctgcaa aacccttcac agaagaagat 1560
tttcaagaaa tgattaaatc tgcacagata atggaaagtc aatatggtca tctttttgac 1620
aaaattataa taaatgatga cctcactgtg gcattcaaaa aaaaaaaaaa aaaaaaaaaa 1680

<210> 38
<211> 560
<212> PRT
<213> homo sapiens

<400> 38
Met Pro Ala Leu Ser Thr Gly Ser Gly Ser Asp Thr Gly Leu Tyr Glu
1 5 10 15
Leu Leu Ala Ala Leu Pro Ala Gln Leu Gln Pro His Val Asp Ser Gln
20 25 30
Glu Asp Leu Thr Phe Leu Trp Asp Met Phe Gly Glu Lys Ser Leu His
35 40 45
Ser Leu Val Lys Ile His Glu Lys Leu His Tyr Tyr Glu Lys Gln Ser
50 55 60
Pro Val Pro Ile Leu His Gly Ala Ala Ala Leu Ala Asp Asp Leu Ala
65 70 75 80
Glu Glu Leu Gln Asn Lys Pro Leu Asn Ser Glu Ile Arg Glu Leu Leu
85 90 95
Lys Leu Leu Ser Lys Pro Asn Val Lys Ala Leu Leu Ser Val His Asp
100 105 110
Thr Val Ala Gln Lys Asn Tyr Asp Pro Val Leu Pro Pro Met Pro Glu
115 120 125
Asp Ile Asp Asp Glu Glu Asp Ser Val Lys Ile Ile Arg Leu Val Lys
130 135 140
Asn Arg Glu Pro Leu Gly Ala Thr Ile Lys Lys Asp Glu Gln Thr Gly
145 150 155 160

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Ala Ile Ile Val Ala Arg Ile Met Arg Gly Gly Ala Ala Asp Arg Ser
                165                 170                 175
Gly Leu Ile His Val Gly Asp Glu Leu Arg Glu Val Asn Gly Ile Pro
            180                 185                 190
Val Glu Asp Lys Arg Pro Glu Glu Ile Ile Gln Ile Leu Ala Gln Ser
        195                 200                 205
Gln Gly Ala Ile Thr Phe Lys Ile Ile Pro Gly Ser Lys Glu Glu Thr
    210                 215                 220
Pro Ser Lys Glu Gly Lys Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
225                 230                 235                 240
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
                245                 250                 255
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
            260                 265                 270
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
        275                 280                 285
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
    290                 295                 300
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser Gly Phe
305                 310                 315                 320
Arg Arg Ser Phe Arg Leu Ser Arg Lys Asp Lys Lys Thr Asn Lys Ser
                325                 330                 335
Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
            340                 345                 350
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
        355                 360                 365
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
    370                 375                 380
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
385                 390                 395                 400
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
                405                 410                 415
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
            420                 425                 430
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
        435                 440                 445
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
    450                 455                 460
Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu Glu Phe Lys
465                 470                 475                 480
Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg Leu Arg Glu
                485                 490                 495
Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp Gln Gly Ala
            500                 505                 510
Ala Lys Pro Phe Thr Glu Glu Asp Phe Gln Glu Met Ile Lys Ser Ala
        515                 520                 525
Gln Ile Met Glu Ser Gln Tyr Gly His Leu Phe Asp Lys Ile Ile Ile
    530                 535                 540
Asn Asp Asp Leu Thr Val Ala Phe Lys Lys Lys Lys Lys Lys Lys Lys
545                 550                 555                 560
```

<210> 39
<211> 1008
<212> DNA
<213> homo sapiens

<400> 39
atgaaacttt tcttccagat gtttatcaaa gccctctttg actataatcc taatgaggat 60
aaggcaattc catgtaagga agctgggctt tctttcaaaa agggagatat tcttcagatt 120
atgagccaag atgatgcaac ttggtggcaa gcgaaacacg aagctgatgc caacccccagg 180
gcaggcttga tcccctcaaa gcatttccag gaaaggagat tggctttgag acgaccagaa 240
atattggttc agcccctgaa agtttccaac aggaaatcat ctggttttag aagaagtttt 300
cgtcttagta gaaaagataa gaaaacaaat aaatccatgt atgaatgcaa gaagagtgat 360
cagtacgaca cagctgacgt acccacatac gaagaagtga caccgtatcg gcgacaaact 420
aatgaaaaat acagactcgt tgtcttggtt ggtcccgtgg gagtagggct gaatgaactg 480
aaacgaaagc tgctgatcag tgacacccag cactatggcg tgacagtgcc ccataccacc 540
agagcaagaa gaagccagga gagtgatggt gttgaataca ttttcatttc caagcatttg 600
tttgagacag atgtacaaaa taacaagttt attgaatatg gagaatataa aaacaactac 660
tacggcacaa gtatagactc agttcggtct gtccttgcta aaaacaaagt ttgtttgttg 720
gatgttcagc ctcatacagt gaagcattta aggacactag aatttaagcc ctatgtgata 780
tttataaagc ctccatcaat agagcgtttg agagaaacaa gaaaaaatgc aaagattatt 840
tcaagcagag atgaccaagg tgctgcaaaa cccttcacag aagaagattt tcaagaaatg 900
attaaatctg cacagataat ggaaagtcaa tatggtcatc tttttgacaa aattataata 960
aatgatgacc tcactgtggc attcaaaaaa aaaaaaaaaa aaaaaaaa 1008

<210> 40
<211> 336
<212> PRT
<213> homo sapiens

<400> 40
Met Lys Leu Phe Phe Gln Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
1 5 10 15
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
20 25 30
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
35 40 45
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
50 55 60
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
65 70 75 80
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser Gly Phe
85 90 95
Arg Arg Ser Phe Arg Leu Ser Arg Lys Asp Lys Lys Thr Asn Lys Ser
100 105 110
Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
115 120 125
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
130 135 140
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
145 150 155 160
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
165 170 175
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
180 185 190
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
195 200 205
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
210 215 220
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
225 230 235 240
Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu Glu Phe Lys

```
                245                 250                 255
Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg Leu Arg Glu
            260                 265                 270
Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp Gln Gly Ala
        275                 280                 285
Ala Lys Pro Phe Thr Glu Glu Asp Phe Gln Glu Met Ile Lys Ser Ala
    290                 295                 300
Gln Ile Met Glu Ser Gln Tyr Gly His Leu Phe Asp Lys Ile Ile Ile
305                 310                 315                 320
Asn Asp Asp Leu Thr Val Ala Phe Lys Lys Lys Lys Lys Lys Lys Lys
                325                 330                 335
```

<210> 41
<211> 636
<212> DNA
<213> homo sapiens

<400> 41

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atgtgctgcc caaagactgc ttgcagaggt cccgtgggag tagggctgaa tgaactgaaa      60
cgaaagctgc tgatcagtga cacccagcac tatggcgtga cagtgcccca taccaccaga     120
gcaagaagaa gccaggagag tgatggtgtt gaatacattt tcatttccaa gcatttgttt     180
gagacagatg tacaaaataa caagtttatt gaatatggag aatataaaaa caactactac     240
ggcacaagta tagactcagt tcggtctgtc cttgctaaaa acaaagtttg tttgttggat     300
gttcagcctc atacagtgaa gcatttaagg acactagaat ttaagcccta tgtgatattt     360
ataaagcctc catcaataga gcgtttgaga gaaacaagaa aaaatgcaaa gattatttca     420
agcagagatg accaaggtgc tgcaaaaccc ttcacagaag aagattttca agaaatgatt     480
aaatctgcac agataatgga aagtcaatat ggtcatcttt ttgacaaaat tataataaat     540
gatgacctca ctgtggcatt caatgagctc aaaacaactt ttgacaaatt agagacagag     600
acccattggg tgccagtgag ctggttacat tcataa                               636
```

<210> 42
<211> 211
<212> PRT
<213> homo sapiens

<400> 42

```
Met Cys Cys Pro Lys Thr Ala Cys Arg Gly Pro Val Gly Val Gly Leu
 1               5                  10                  15
Asn Glu Leu Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly
            20                  25                  30
Val Thr Val Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp
        35                  40                  45
Gly Val Glu Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val
    50                  55                  60
Gln Asn Asn Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr
65                  70                  75                  80
Gly Thr Ser Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val
                85                  90                  95
Cys Leu Leu Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu
            100                 105                 110
Glu Phe Lys Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg
        115                 120                 125
Leu Arg Glu Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp
    130                 135                 140
Gln Gly Ala Ala Lys Pro Phe Thr Glu Glu Asp Phe Gln Glu Met Ile
145                 150                 155                 160
```

```
Lys Ser Ala Gln Ile Met Glu Ser Gln Tyr Gly His Leu Phe Asp Lys
                165                 170                 175
Ile Ile Ile Asn Asp Asp Leu Thr Val Ala Phe Asn Glu Leu Lys Thr
            180                 185                 190
Thr Phe Asp Lys Leu Glu Thr Glu Thr His Trp Val Pro Val Ser Trp
        195                 200                 205
Leu His Ser
    210
```

<210> 43
<211> 723
<212> DNA
<213> homo sapiens

<400> 43

```
atgtatgaat gcaagaagag tgatcagtac gacacagctg acgtacccac atacgaagaa      60
gtgacaccgt atcggcgaca aactaatgaa aaatacagac tcgttgtctt ggttggtccc     120
gtgggagtag ggctgaatga actgaaacga aagctgctga tcagtgacac ccagcactat     180
ggcgtgacag tgccccatac caccagagca agaagaagcc aggagagtga tggtgttgaa     240
tacattttca tttccaagca tttgtttgag acagatgtac aaaataacaa gtttattgaa     300
tatggagaat ataaaaacaa ctactacggc acaagtatag actcagttcg gtctgtcctt     360
gctaaaaaca aagtttgttt gttggatgtt cagcctcata cagtgaagca tttaaggaca     420
ctagaattta agccctatgt gatatttata aagcctccat caatagagcg tttgagagaa     480
acaagaaaaa atgcaaagat tatttcaagc agagatgacc aaggtgctgc aaaacccttc     540
acagaagaag attttcaaga aatgattaaa tctgcacaga taatggaaag tcaatatggt     600
catcttttg acaaaattat aataaatgat gacctcactg tggcattcaa tgagctcaaa     660
acaacttttg acaaattaga gacagagacc cattgggtgc cagtgagctg gttacattca     720
taa                                                                  723
```

<210> 44
<211> 240
<212> PRT
<213> homo sapiens

<400> 44

```
Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
 1               5                  10                  15
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
            20                  25                  30
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
        35                  40                  45
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
    50                  55                  60
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
65                  70                  75                  80
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
                85                  90                  95
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
            100                 105                 110
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
        115                 120                 125
Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu Glu Phe Lys
    130                 135                 140
Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg Leu Arg Glu
145                 150                 155                 160
Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp Gln Gly Ala
```

```
                165                 170                 175
Ala Lys Pro Phe Thr Glu Glu Asp Phe Gln Glu Met Ile Lys Ser Ala
            180                 185                 190
Gln Ile Met Glu Ser Gln Tyr Gly His Leu Phe Asp Lys Ile Ile Ile
        195                 200                 205
Asn Asp Asp Leu Thr Val Ala Phe Asn Glu Leu Lys Thr Thr Phe Asp
    210                 215                 220
Lys Leu Glu Thr Glu Thr His Trp Val Pro Val Ser Trp Leu His Ser
225                 230                 235                 240
```

<210> 45
<211> 1731
<212> DNA
<213> homo sapiens

<400> 45

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atgccagctt tgtcaacggg atctgggagt gacactggtc tgtatgagct gttggctgct      60
ctgccagccc agctgcagcc acatgtggat agccaggaag acctgacctt cctctgggat     120
atgtttggtg aaaaaagcct gcattcattg gtaaagattc atgaaaaact acactactat     180
gagaagcaga gtccggtgcc cattctccat ggtgcggcgg ccttggccga tgatctggcc     240
gaagagcttc agaacaagcc attaaacagt gagatcagag agctgttgaa actactgtca     300
aaacccaatg tgaaggcttt gctctctgta catgatactg tggctcagaa gaattacgac     360
ccagtgttgc ctcctatgcc tgaagatatt gacgatgagg aagactcagt aaaaataatc     420
cgtctggtca aaaatagaga accactggga gctaccatta agaaggatga acagaccggg     480
gcgatcattg tggccagaat catgagagga ggagctgcag atagaagtgg tcttattcat     540
gttggtgatg aacttaggga agtcaacggg ataccagtgg aggataaaag gcctgaggaa     600
ataatacaga ttttggctca gtctcaggga gcaattacat ttaagattat acccggcagc     660
aaagaggaga caccatcaaa agaaggcaag atgtttatca aagccctctt tgactataat     720
cctaatgagg ataaggcaat tccatgtaag gaagctgggc tttctttcaa aaagggagat     780
attcttcaga ttatgagcca agatgatgca acttggtggc aagcgaaaca cgaagctgat     840
gccaacccca gggcaggctt gatcccctca aagcatttcc aggaaaggag attggctttg     900
agacgaccag aaatattggt tcagcccctg aaagtttcca acaggaaatc atctggtttt     960
agaagaagtt ttcgtcttag tagaaaagat aagaaaacaa ataaatccat gtatgaatgc    1020
aagaagagtg atcagtacga cacagctgac gtacccacat acgaagaagt gacaccgtat    1080
cggcgacaaa ctaatgaaaa atacagactc gttgtcttgg ttggtcccgt gggagtaggg    1140
ctgaatgaac tgaaacgaaa gctgctgatc agtgacaccc agcactatgg cgtgacagtg    1200
ccccatacca ccagagcaag aagaagccag gagagtgatg gtgttgaata cattttcatt    1260
tccaagcatt tgtttgagac agatgtacaa aataacaagt ttattgaata tggagaatat    1320
aaaaacaact actacggcac aagtatagac tcagttcggt ctgtccttgc taaaaacaaa    1380
gtttgtttgt tggatgttca gcctcataca gtgaagcatt taaggacact agaatttaag    1440
ccctatgtga tatttataaa gcctccatca atagagcgtt tgagagaaac aagaaaaaat    1500
gcaaagatta tttcaagcag agatgaccaa ggtgctgcaa aacccttcac agaagaagat    1560
tttcaagaaa tgattaaatc tgcacagata atggaaagtc aatatggtca tctttttgac    1620
aaaattataa taaatgatga cctcactgtg gcattcaatg agctcaaaac aacttttgac    1680
aaattagaga cagagaccca ttgggtgcca gtgagctggt tacattcata a             1731
```

<210> 46
<211> 576
<212> PRT
<213> homo sapiens

<400> 46

```
Met Pro Ala Leu Ser Thr Gly Ser Gly Ser Asp Thr Gly Leu Tyr Glu
 1               5                  10                  15
Leu Leu Ala Ala Leu Pro Ala Gln Leu Gln Pro His Val Asp Ser Gln
            20                  25                  30
```

```
Glu Asp Leu Thr Phe Leu Trp Asp Met Phe Gly Glu Lys Ser Leu His
      35                  40                  45
Ser Leu Val Lys Ile His Glu Lys Leu His Tyr Tyr Glu Lys Gln Ser
    50                  55                  60
Pro Val Pro Ile Leu His Gly Ala Ala Ala Leu Ala Asp Asp Leu Ala
65                  70                  75                  80
Glu Glu Leu Gln Asn Lys Pro Leu Asn Ser Glu Ile Arg Glu Leu Leu
                85                  90                  95
Lys Leu Leu Ser Lys Pro Asn Val Lys Ala Leu Leu Ser Val His Asp
            100                 105                 110
Thr Val Ala Gln Lys Asn Tyr Asp Pro Val Leu Pro Pro Met Pro Glu
        115                 120                 125
Asp Ile Asp Asp Glu Glu Asp Ser Val Lys Ile Ile Arg Leu Val Lys
    130                 135                 140
Asn Arg Glu Pro Leu Gly Ala Thr Ile Lys Lys Asp Glu Gln Thr Gly
145                 150                 155                 160
Ala Ile Ile Val Ala Arg Ile Met Arg Gly Gly Ala Ala Asp Arg Ser
                165                 170                 175
Gly Leu Ile His Val Gly Asp Glu Leu Arg Glu Val Asn Gly Ile Pro
            180                 185                 190
Val Glu Asp Lys Arg Pro Glu Glu Ile Ile Gln Ile Leu Ala Gln Ser
        195                 200                 205
Gln Gly Ala Ile Thr Phe Lys Ile Ile Pro Gly Ser Lys Glu Glu Thr
    210                 215                 220
Pro Ser Lys Glu Gly Lys Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
225                 230                 235                 240
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
                245                 250                 255
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
            260                 265                 270
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
        275                 280                 285
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
    290                 295                 300
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser Gly Phe
305                 310                 315                 320
Arg Arg Ser Phe Arg Leu Ser Arg Lys Asp Lys Lys Thr Asn Lys Ser
                325                 330                 335
Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
            340                 345                 350
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
        355                 360                 365
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
    370                 375                 380
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
385                 390                 395                 400
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
                405                 410                 415
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
            420                 425                 430
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
        435                 440                 445
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
    450                 455                 460
Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu Glu Phe Lys
465                 470                 475                 480
```

```
Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg Leu Arg Glu
                485                 490                 495
Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp Gln Gly Ala
            500                 505                 510
Ala Lys Pro Phe Thr Glu Glu Asp Phe Gln Glu Met Ile Lys Ser Ala
        515                 520                 525
Gln Ile Met Glu Ser Gln Tyr Gly His Leu Phe Asp Lys Ile Ile Ile
    530                 535                 540
Asn Asp Asp Leu Thr Val Ala Phe Asn Glu Leu Lys Thr Thr Phe Asp
545                 550                 555                 560
Lys Leu Glu Thr Glu Thr His Trp Val Pro Val Ser Trp Leu His Ser
                565                 570                 575
```

<210> 47
<211> 1059
<212> DNA
<213> homo sapiens

<400> 47

```
atgaaacttt tcttccagat gtttatcaaa gccctctttg actataatcc taatgaggat      60
aaggcaattc catgtaagga agctgggctt tctttcaaaa agggagatat tcttcagatt     120
atgagccaag atgatgcaac ttggtggcaa gcgaaacacg aagctgatgc caaccccagg     180
gcaggcttga tcccctcaaa gcatttccag gaaaggagat tggctttgag acgaccagaa     240
atattggttc agcccctgaa agtttccaac aggaaatcat ctggttttag aagaagtttt     300
cgtcttagta gaaaagataa gaaaacaaat aaatccatgt atgaatgcaa gaagagtgat     360
cagtacgaca cagctgacgt acccacatac gaagaagtga caccgtatcg gcgacaaact     420
aatgaaaaat acagactcgt tgtcttggtt ggtcccgtgg gagtagggct gaatgaactg     480
aaacgaaagc tgctgatcag tgacacccag cactatggcg tgacagtgcc ccataccacc     540
agagcaagaa gaagccagga gagtgatggt gttgaataca ttttcatttc caagcatttg     600
tttgagacag atgtacaaaa taacaagttt attgaatatg gagaatataa aaacaactac     660
tacggcacaa gtatagactc agttcggtct gtccttgcta aaaacaaagt ttgtttgttg     720
gatgttcagc ctcatacagt gaagcattta aggacactag aatttaagcc ctatgtgata     780
tttataaagc ctccatcaat agagcgtttg agagaaacaa gaaaaaatgc aaagattatt     840
tcaagcagag atgaccaagg tgctgcaaaa cccttcacag aagaagattt tcaagaaatg     900
attaaatctg cacagataat ggaaagtcaa tatggtcatc tttttgacaa aattataata     960
aatgatgacc tcactgtggc attcaatgag ctcaaaacaa cttttgacaa attagagaca    1020
gagacccatt gggtgccagt gagctggtta cattcataa                           1059
```

<210> 48
<211> 352
<212> PRT
<213> homo sapiens

<400> 48

```
Met Lys Leu Phe Phe Gln Met Phe Ile Lys Ala Leu Phe Asp Tyr Asn
 1               5                  10                  15
Pro Asn Glu Asp Lys Ala Ile Pro Cys Lys Glu Ala Gly Leu Ser Phe
            20                  25                  30
Lys Lys Gly Asp Ile Leu Gln Ile Met Ser Gln Asp Asp Ala Thr Trp
        35                  40                  45
Trp Gln Ala Lys His Glu Ala Asp Ala Asn Pro Arg Ala Gly Leu Ile
    50                  55                  60
Pro Ser Lys His Phe Gln Glu Arg Arg Leu Ala Leu Arg Arg Pro Glu
65                  70                  75                  80
Ile Leu Val Gln Pro Leu Lys Val Ser Asn Arg Lys Ser Ser Gly Phe
                85                  90                  95
```

```
Arg Arg Ser Phe Arg Leu Ser Arg Lys Asp Lys Lys Thr Asn Lys Ser
            100                 105                 110
Met Tyr Glu Cys Lys Lys Ser Asp Gln Tyr Asp Thr Ala Asp Val Pro
        115                 120                 125
Thr Tyr Glu Glu Val Thr Pro Tyr Arg Arg Gln Thr Asn Glu Lys Tyr
    130                 135                 140
Arg Leu Val Val Leu Val Gly Pro Val Gly Val Gly Leu Asn Glu Leu
145                 150                 155                 160
Lys Arg Lys Leu Leu Ile Ser Asp Thr Gln His Tyr Gly Val Thr Val
                165                 170                 175
Pro His Thr Thr Arg Ala Arg Arg Ser Gln Glu Ser Asp Gly Val Glu
            180                 185                 190
Tyr Ile Phe Ile Ser Lys His Leu Phe Glu Thr Asp Val Gln Asn Asn
        195                 200                 205
Lys Phe Ile Glu Tyr Gly Glu Tyr Lys Asn Asn Tyr Tyr Gly Thr Ser
    210                 215                 220
Ile Asp Ser Val Arg Ser Val Leu Ala Lys Asn Lys Val Cys Leu Leu
225                 230                 235                 240
Asp Val Gln Pro His Thr Val Lys His Leu Arg Thr Leu Glu Phe Lys
                245                 250                 255
Pro Tyr Val Ile Phe Ile Lys Pro Pro Ser Ile Glu Arg Leu Arg Glu
            260                 265                 270
Thr Arg Lys Asn Ala Lys Ile Ile Ser Ser Arg Asp Asp Gln Gly Ala
        275                 280                 285
Ala Lys Pro Phe Thr Glu Glu Asp Phe Gln Glu Met Ile Lys Ser Ala
    290                 295                 300
Gln Ile Met Glu Ser Gln Tyr Gly His Leu Phe Asp Lys Ile Ile Ile
305                 310                 315                 320
Asn Asp Asp Leu Thr Val Ala Phe Asn Glu Leu Lys Thr Thr Phe Asp
                325                 330                 335
Lys Leu Glu Thr Glu Thr His Trp Val Pro Val Ser Trp Leu His Ser
            340                 345                 350
```

<210> 49
<211> 1906
<212> DNA
<213> homo sapiens

<400> 49

```
tgcccgcgga ccgcggcagc ccagagcaga aacggcttac aaaatataca gatcttggta      60
gacaacgtgg ctgcaggctg ttgaattgga attccctgtg gctgtccgaa ggcagggtgt     120
ccggagagcg gtgggctgac ctgttcctac accttgcatc atgccagctt tgtcaacggg     180
atctgggagt gacactggtc tgtatgagct gttggctgct ctgccagccc agctgcagcc     240
acatgtggat agccaggaag acctgacctt cctctgggat atgtttggtg aaaaaagcct     300
gcattcattg gtaaagattc atgaaaaact acactactat gagaagcaga gtccggtgcc     360
cattctccat ggtgcggcgg ccttggccga tgatctggcc gaagagcttc agaacaagcc     420
attaaacagt gagatcagag agctgttgaa actactgtca aaacccaatg tgaaggcttt     480
gctctctgta catgatactg tggctcagaa gaattacgac ccagtgttgc ctcctatgcc     540
tgaagatatt gacgatgagg aagactcagt aaaaataatc cgtctggtca aaaatagaga     600
accactggga gctaccatta agaaggatga acagaccggg gcgatcattg tggccagaat     660
catgagagga ggagctgcag atagaagtgg tcttattcat gttggtgatg aacttaggga     720
agtcaacggg ataccagtgg aggataaaag gcctgaggaa ataatacaga ttttggctca     780
gtctcaggga gcaattacat ttaagattat acccggcagc aaagaggaga caccatcaaa     840
agaaggcaag atgtttatca aagccctctt tgactataat cctaatgagg ataaggcaat     900
tccatgtaag gaagctgggc tttctttcaa aaagggagat attcttcaga ttatgagcca     960
agatgatgca acttggtggc aagcgaaaca cgaagctgat gccaacccca gggcaggctt    1020
```

gatcccctca aagcatttcc aggaaaggag attggctttg agacgaccag aaatattggt 1080
tcagcccctg aaagtttcca acaggaaatc atctggtttt agaagaagtt ttcgtcttag 1140
tagaaaagat aagaaaacaa ataaatccat gtatgaatgc aagaagagtg atcagtacga 1200
cacagctgac gtacccacat acgaagaagt gacaccgtat cggcgacaaa ctaatgaaaa 1260
atacagactc gttgtcttgg ttggtcccgt gggagtaggg ctgaatgaac tgaaacgaaa 1320
gctgctgatc agtgacaccc agcactatgg cgtgacagtg ccccatacca ccagagcaag 1380
aagaagccag gagagtgatg gtgttgaata cattttcatt tccaagcatt tgtttgagac 1440
agatgtacaa aataacaagt ttattgaata tggagaatat aaaaacaact actacggcac 1500
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